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Mechanisms of Behavioral Change Targeting Automatic Processes

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Mechanisms of Behavioral Change Targeting Automatic Processes

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Mechanisms of Behavioral Change Targeting Automatic Processes

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In order to eliminate unhealthy behaviors, one must find ways to make better choices. Changing preferences is an important strategy in addressing public health concerns such as the obesity epidemic. In this dissertation, I present several lines of research, which all aim to influence choice behavior. First, we developed a novel extensive training paradigm that uses monetary reinforcement to influence choices for less desired palatable foods over initially more preferred foods. We found that, as reinforced training progressed, there was decreased recruitment of a frontoparietal network of brain regions that have been previously associated with cognitive control. We also found neural evidence that suggests formation of a stronger stimulus-response association as reinforced training progressed. These findings demonstrate that it is possible to influence food choices through reinforcement and that training is associated with a decreasing need for top-down frontoparietal control. However, the long

term durability of this change in choice behavior is in question. Learning theory predicts a return to choosing the initially more preferred item simply with the passage of time, despite overtraining the new behavior. Thus, we turned our efforts toward targeting automatic processes to achieve a lasting shift in choice behavior. We found that our attempts to interfere with memory traces for an established choice or to train bottom-up inhibition to avoid particular food items were unsuccessful. However, we found that driving sustained attention toward particular food items at behaviorally relevant points in time during cue-approach training robustly influences choice preferences in favor of those items. Imaging results show that value representation for those items in the ventromedial prefrontal cortex is amplified. Finally, we found that spacing cue-approach training trials over multiple days benefits the long-term maintenance of the cue-approach choice effect. Results presented in this dissertation lay the groundwork for new insights into mechanisms of behavioral change and value-based decision making more broadly as well as suggest some strategies for developing real-world intervention paradigms to help those seeking to adopt and maintain healthier habits.

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Chapter 1

Introduction

In order to achieve lasting behavioral change to improve health, one must overcome the automaticity and strength of first-learned habits. First-learned behaviors are the rule that must be broken by subsequent learning in order for new habits to replace older ones over the long term (Bouton, 2004). Initial positive change in behavior may be achieved through intervention based on willful effort, but the long term prospects for such improvement are uncertain. Recent focus has turned to targeting automatic processes to change human behavior with the goal of preventing disease (Marteau et al., 2012).

Various ways to achieve lasting behavioral change have been investigated and they are presented in this dissertation. First, we probed the neural mechanisms involved in forming a new behavior via reinforcement learning using a contingency management paradigm. Next, we focused our efforts on targeting automatic processes to achieve behavioral change without relying on external reinforcement. We set out to weaken old behavior via memory updating during reconsolidation and training inhibition of behavior. We also sought to strengthen new behavior via novel non-reinforced training (Schon-

berg et al., 2014a) and to better understand the neural mechanisms underlying non-reinforced training and subsequent change in choice behavior.

1.1 First-learned vs. second-learned behaviors

Growing evidence from the field of learning and memory suggests that the ineffectiveness of long-term behavioral change may stem from a fundamental feature of learning termed the "recency-primacy shift" (which is the human analog to "spontaneous recovery" in animals). First-learned responses to a particular stimulus become stronger with time after extinction, whereas second-learned responses become increasingly weaker with the passage of time. These findings have been found in animals using fear conditioning (Bouton, 1993) and in humans using a motor skill as well as a verbal learning task (Bjork, 2001). Spontaneous recovery provides substantial evidence that first-learned responses are not erased, but merely suppressed in favor of later learned responses. If indeed early responses are not erased, they can be revived at a later time. Furthermore, evidence shows that second-learned behaviors are much more contextually specific than first-learned behaviors and may not generalize to new contexts (be it spatial, temporal or internal state), which instead cue the first-learned response. Thus a first-learned behavior seems to be more powerful and flexible than any subsequently learned behavior (Bouton, 2004). First-learned behaviors are in a sense the rule, and any subsequently-learned behavior is an exception to that rule. Given the discrepancy in strength between first- and second-learned behaviors, we sought to strengthen later-

learned behavior using traditional reinforcement learning, but we also set out to target automatic processes to either weaken first-learned behavior or to enhance later-learned responses without relying on external reinforcement.

1.2 Contingency management

Contingency management is a strategy often used in the treatment of drug abuse. It involves positive reinforcement for desired behavior (e.g. abstinence) and sometimes punishment for undesired behavior (e.g. drug use). Positive reinforcement often takes the form of vouchers, money or drug doses while punishment could take the form of a negative report to a parole officer, for example (Petry, 2000). This strategy has been successfully used in the treatment of abusers of alcohol (Petry et al., 2000), marijuana (Budney et al., 1991), benzodiazapines (Stitzer et al., 1992) and nicotine (Shoptaw et al., 1996), leading to reduced consumption and better attendance at therapy sessions. However, the effectiveness of this strategy in the long run, once reinforcement is no longer provided, is open to question. Follow up studies on the efficacy of contingency management have found a high incidence of relapse (Higgins et al., 1995). Additionally, a meta-analysis of nineteen studies using incentives to help participants quit smoking found that only one study demonstrated significantly higher quit rates for the incentives group than for the control group beyond the six-month assessment (Cahill and Perera, 2011).

Contingency management-style procedures may be very useful in encouraging individuals to maintain new, healthier behaviors. Using incentives

to reinforce certain behaviors could provide a useful tool for the study of acquisition and resilience of new habits. In the studies presented in Chapter 2, we used reinforcement learning in a contingency management-style procedure to induce a shift in preference. We also investigated the neural substrates that support such a shift in choice preference following a reinforcement learning procedure.

1.3 Ineffectiveness of will power

Human behavior is balanced between two categories of behaviors. The first is reflective, effortful and flexible goal-directed behavior. The second is automatic and rigid habitual behavior (Balleine and O'Doherty, 2010). These two categories of behavior interact and often complement one another, but they sometimes come into conflict. Because of the automaticity of habitual behavior and its lower cost, it often drives action despite a conflicting goal, especially under distraction or stress.

Many behavioral change paradigms have been developed to try and address the problem faced by individuals who are incapable of maintaining improved behavior, but most rely on exerting will power. Research has shown that such effortful control is fragile, likely to crumble when under stress or faced with distractions, which may explain the limited success of initiatives such as diets (Wood and Neal, 2007). Additionally, the concept of ego depletion (Baumeister et al., 1998) suggests that executive control is a limited resource and that exerting much of it in one domain makes it more difficult to exert

it in other domains. Although there has been work on training of executive control and avoidance of ego depletion (Thorell et al., 2009), this strategy still relies on exertion of effort and is unlikely to counter the automaticity of habits in the long run. Thus, relying on effortful control of behavior seems to be a maladapted strategy for maintenance of behavioral change. Therefore efforts should concentrate on alternative strategies for the replacement of bad habits with more desirable ones.

1.4 Targeting automatic processes for behavioral change

1.4.1 Weakening first-learned behavior

Despite some evidence that contingency management can be successful in changing behavior, it is unclear how long the new behavior can be expected to last. Thus there should be greater focus on more automatic mechanisms that strengthen new behavior and/or weaken older ones.

1.4.1.1 Memory reconsolidation

Weakening a memory trace could prove to be a useful mechanism to achieve the goal of weakening old behavior. When reinstated, established memories enter a labile state that renders them susceptible to updating. These memories then "reconsolidate" in order to persist (Nader et al., 2000). Memory updating during reconsolidation has been demonstrated in many species using several different memory paradigms, suggesting that this process is a fundamental feature that spans different kinds of memory (see Besnard et al.,

2012; Alberini and Ledoux, 2013; Reichelt and Lee, 2013, for review).

Memory updating during reconsolidation has been attempted in the treatment of post traumatic stress disorder using pharmaceuticals (PTSD, Debiec and Ledoux, 2006; Brunet et al., 2008). Schiller et al. (2010) used a non-invasive behavioral retrieval-extinction paradigm to demonstrate long term disruption in the return of fear in healthy humans. Non-invasive behavioral paradigms have also been effective in reducing drug-seeking behavior in human addicts (Xue et al., 2012). However, to our knowledge, this strategy has not been widely adopted for more common behavioral change goals. Disrupting memories during reconsolidation shows great promise for the development of new behavioral change paradigms. In the studies described in Chapter 3, we employed a modified behavioral paradigm to that employed by Schiller et al. (2010) with the goal to update a common appetitive behavior.

1.4.1.2 Trained inhibition

Inhibiting alternative courses of action is often required to reach particular goals. Researchers often measure 'response inhibition', which is the overriding or canceling of a planned action. Response inhibition is often measured using the go/nogo or stop-signal tasks. In the latter, participants must inhibit a prepotent response when a cue appears. Inhibition can be trained to be more effective. This is especially true in light of the fact that that response inhibition is not always a "top-down" process. In fact, automatic "bottom-up" inhibition can be achieved after a cue to inhibit an action (stop-signal)

is consistently associated with specific stimuli (Verbruggen and Logan, 2008; Lenartowicz et al., 2011). Training inhibition could prove useful to achieve lasting behavioral change by targeting automatic inhibitory processes. Thus, in the studies presented in Chapter 4, we sought to elicit an automatic inhibitory signal to particular stimuli. We hypothesized that participants would avoid choosing items that elicited such automatic inhibition.

1.4.2 Strengthening second-learned behavior

In another approach, rather than weaken old responses, we sought to strengthen new behavior by increasing the value of particular choice options. Earlier research in cognitive psychology has mainly relied on reinforcement learning in order to influence value (Thorndike, 1911; O'Doherty et al., 2004). In parallel, research in behavioral economics has mainly relied on framing of decisions (Tversky and Kahneman, 1986; Slovic, 1995; De Martino et al., 2006) and altering the architecture of the choice environment (Thaler and Sunstein, 2008) in order to influence value. However, little research has been conducted to attempt to directly perturb the value of goods.

Schonberg et al. (2014a) have developed a simple manipulation that boosts subjective value placed on appetitive junk food items without relying on habitual responding or altering the description of the decision problem. The manipulation consists of 'Go' training, designed as the functional mirror to the cued inhibition version of the stop-signal task (Verbruggen and Logan, 2008). Images of snack food items appeared one at a time on a computer screen.

Participants were asked to passively view most items, but for 25% of the items, an auditory cue sounded a short time after the image appeared on the screen as a signal that participants were to press a key on the keyboard. Following the training phase, participants made binary decisions, choosing which item they would like to eat at the end of the experiment. In pairs of Go and control (i.e. NoGo) items that were matched for pre-experimental subjective value for each participant, Go items were reliably chosen over NoGo items in five independent samples of participants. fMRI results point to amplification of the value signal for Go items in the ventromedial prefrontal cortex (vmPFC), a brain region heavily implicated in valuation (Plassmann et al., 2007; Tom et al., 2007; Chib et al., 2009; McNamee et al., 2013), rather than a shift in value following the manipulation.

The cue-approach training task offers potential for translational extensions. This paradigm is relevant for individuals interested in losing weight, for example. Rather than dieting, one might be able to employ a training exercise that could help increase the appeal of healthy foods. However, the exact neural mechanism engaged during cue-approach training responsible for a preference shift toward Go items remains poorly understood. In an fMRI study presented in Chapter 5, we employ advanced neuroimaging techniques including machine learning methods to gain insight into the neural mechanism of action during cue-approach training.

1.5 Long-term maintenance of behavioral change

The main challenge facing any behavioral change paradigm is long term maintenance. Although targeting automatic processes rather than relying on reinforcement to achieve behavioral change is likely to be more successful in the long run (Marteau et al., 2012), strategies to further ensure the long-term durability of any change in behavior are worth exploring. Given the importance of context in habit learning (Bouton, 2004), one strategy that could be employed lies in training across a broad range of spatial contexts to increase its generalization. Varying context during training should help the resilience of the second response as the latter seems to be context-specific. Contextual variability has been attempted in the treatment of phobias (Vansteenwegen et al., 2007). Arachnophobic individuals received exposure therapy in either a single room or in three distinct rooms. Participants who received exposure therapy in multiple rooms had lower arousal (as measured by skin conductance) to spiders in a new room when compared to those who received exposure therapy in a single room. Although this strategy has been successful in the fear domain, it does not seem to have been attempted with a view to improving the sustainability of behavioral change in the appetitive domain and is worth pursuing in future research.

Another strategy that could be adopted to strengthen the memory trace of a new response is spacing training trials over time. Meta-analysis of the distributed practice effect in verbal learning tasks revealed that spaced (vs. massed) learning of items consistently leads to better retention (Cepeda et al.,

2006). The basis of the distributed practice effect is thought to lie in the difficulty of retrieval. Indeed, retrieval has been shown to be a powerful encoding event (Benjamin and Tullis, 2010). The more difficult the retrieval, the more powerful the encoding event seems to be. Retrieving a prior study event that is more distant in time is more difficult than retrieving one that is closer. This strategy has been adopted in the treatment of phobias. Tsao and Kraske (2000) distributed exposure therapy sessions over multiple days, and showed that this schedule was beneficial for blocking the return of fear. However, spacing has scarcely been employed in behavioral change paradigms in the appetitive domain. Thus, we sought to distribute cue-approach training trials over multiple days in studies in Chapter 6 to test the effect of this training schedule on the long term maintenance of the preference shift induced by cue-approach training.

In the following chapters, I lay out the rationale, procedures and results for five research projects that all aim to achieve a shift in behavior. In each project, we employed a different strategy to either weaken old behavior or strengthen new behavior. We have had varying success employing the different strategies to achieve a shift in choice behavior and for the most successful we also investigated the neural mechanism responsible for behavioral change, primarily using functional magnetic resonance imaging (fMRI).

Chapter 2

Reinforced training of choice behavior

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Contribution of authors: TM and AB contributed equally to this work. TM, AB and RAP designed the study and wrote the paper; TM, AB and JAM analyzed the data and TM, AB and AMH collected the data.

2.1 Introduction

Changing individual food preferences is a key step to solving a broad range of challenges in public health. This problem is most obvious in the current epidemic of obesity in the United States. In the period spanning 1999 to 2008, about one third of the American population was obese and another third was overweight (Flegal et al., 2010), placing these individuals at high risk for a broad range of chronic medical conditions, including cardiovascular diseases, diabetes, and cancer. The ability to reduce preferences for highly palatable processed foods is essential to solving these public health problems.

Recent studies explored the brain mechanisms of self-control in the domain of food items. Hare et al. (2009) found that dieters exhibited greater activation of several regions, among them the left dorsolateral prefrontal cortex (dlPFC) when they were asked to focus on the health rather than the taste aspect of food items. The authors hypothesized that successful self-control might relate to the extent to which the dlPFC can modulate the activity of the ventromedial PFC, an area implicated in valuation of stimuli (e.g. Chib et al., 2009; Rangel and Hare; Rushworth et al., 2011). In another study with healthy participants the same group (Hare et al., 2011) found that activity in the left dlPFC correlated with the health aspects of food items rather than their taste. These studies measured the effects of directing attention to different features of food items but did not use conditioning to induce preference changes. Tricomi et al. (2009) performed an extensive training procedure in humans and showed that by repeatedly choosing a certain food item in sessions spanning 3 days, participants were no longer sensitive to the value of that option after selective satiation compared to a non-satiated one. Following findings in animals (Yin et al., 2004), the authors focused their analysis on the dorsolateral striatum and showed an increase in its activity as training progressed and responses became more habitual. A recent study (Wunderlich et al., 2012) corroborated these results by using an extensive training two-armed-bandit task that also showed a similar pattern of activity in the dorsolateral striatum using abstract (non-food) stimuli. However, no study attempted to influence the preference of healthy participants when choosing between two food items that initially

have different values.

In the current study we assessed participants' individual preferences of palatable junk food items (Plassmann et al., 2007) and developed an extensive training paradigm to enhance choice behavior of less-preferred items over more favorable ones. We first show, behaviorally, that after extensive training, subjects are more likely to choose items that they formerly placed less value on compared to untrained items. In an independent sample we replicate this behavioral finding and examine the underlying neural substrates of extensive training. Based on the above-mentioned studies we hypothesized a two-sided process will occur during training reflecting a shift from goal-directed to more habit-like responding. On the one hand, we will observe increased activity of dorsolateral striatum with training, reflecting the increased involvement of sensorimotor striatum in habitual responding. On the other hand, there will be a decrease in activity with repeated choices of the less preferred option in the control network including the dlPFC and other regions (Dosenbach et al., 2006, 2007). We also hypothesized we will observe changes in the connectivity with dlPFC as has been reported by Hare et al. (2009, 2011), reflecting decreasing need for top-down control with practice and stronger reliance on stimulus-response associations.

2.2 Materials and Methods

2.2.1 Participants

A total of fifty healthy participants took part in 2 separate studies. Twenty-nine participants completed the behavioral experiment out of which data from 28 (22 female; mean age, 20.3 ± 1.5; range, 18-24. Mean Body Mass Index (BMI) = 21.6 ± 3.22) are included in the analysis reported below (one participant was excluded due to auction exclusion criteria - see below under behavioral analysis). Twenty-one right-handed participants completed the imaging version. Data from 17 participants (8 female; mean age, 22.4 ± 3.6; range, 18-30. Mean BMI = 25 ± 4.1) are reported in the imaging analyses (one participant was excluded due to auction exclusion criteria, 3 others due to task analysis exclusion criteria - see below under imaging analysis). All subjects had normal or corrected-to-normal vision, no history of psychiatric diagnoses, neurologic or metabolic illnesses, no history of eating disorders, had no food restrictions, and were not taking any medications that would interfere with the experiment. Additionally, participants who were scanned were free of any metal implants or any other contraindications for MRI. Participants were told that the goal of the experiment was to study food preferences and were asked to refrain from eating 4 hours prior to arrival to the laboratory (Plassmann et al., 2007). All participants gave informed consent and the internal review board (IRB) at the University of Texas at Austin approved the study.

2.2.2 Task

For the general procedure of the task see Figure 2.1. Participants first underwent an auction (Figure 2.1A), then a training task (Figure 2.1B), then a probe (Figure 2.1C) and a repeat of the auction (Figure 2.1D).

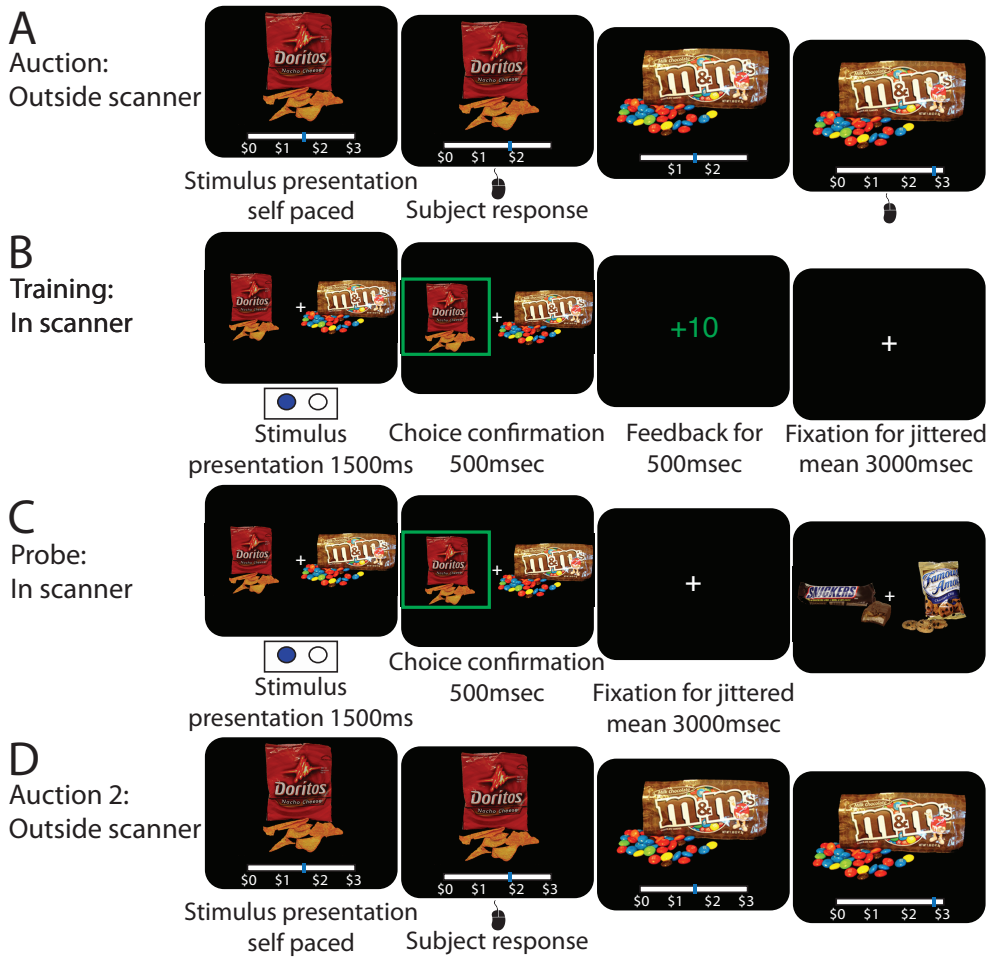

Figure 2.1: *Task procedure showing the different stages on the left panel and the different task stages in the right panel: A) Auction; B) Training (timings refer to imaging version); C) Probe (timings refer to imaging version); D) Auction repeat.*

2.2.2.1 Auction

First, participants took part in an auction (Becker et al., 1964) (Figure 2.1A) in which photographs of 60 appetitive junk food items (Plassmann et al., 2007) were presented. Participants were endowed with three dollars and told that they could have an opportunity to use them to buy a snack at the end of the session. During the auction, participants were presented with one item at a time on a computer screen. They placed their bid by moving the mouse cursor along an analog scale that spanned from 0 to 3 at the bottom of the screen. The auction was self-paced and the next item was presented only after the participants placed their bid. This procedure has been shown to reliably obtain a measure of willingness to pay per item (WTP) (for a full description see Plassmann et al., 2007). Two participants (one from each study) were excluded because they bid less than $0.25 on more than 45 items; this was done to ensure a sufficient number of highly-valued items for the pairing procedure (see below).

2.2.2.2 Training

Behavioral Version. The items were divided into 30 lower value and 30 higher value items according to a median split of each individual participants' bids (Figure 2.2A). Each item within the higher value and lower value splits was then ranked (H1-H30 and L1-L30) and pairs were created to ensure the largest possible gap in WTP by pairing H1 with L1, H2 with L2, etc. (2.2B). These 30 pairs were then divided into 3 sets of 10 pairs by selecting every

third pair starting from the first, second or third pair. One of these pair sets was chosen for the training task as Train Low pairs, another was used for the probe as Untrained pairs and the last was only used for the 2nd auction. Pair set assignments were randomized across participants.

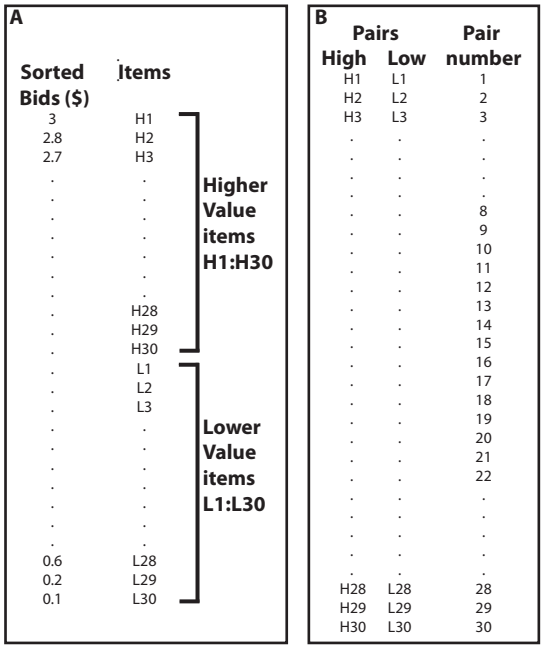

Figure 2.2: *Diagram of the sorting and pairing procedure. A) Bids during the auction were sorted from highest to the lowest. Rank ordered items were then split in half based on subjective individual preferences to Higher (H1:H30) and Lower (L1:L30) value items. B) Pairs of items were created such that items has a gap of 30 items between them. The highest High value item was paired with the Highest low item, e.g. H1:L1, H2:L2 etc.*

During training, participants were shown 2 items and told to choose one item on each trial and that some of the choices would earn them points that would later be converted to money (each point was worth 1 cent). Unbeknownst to the participants, the only rewarded choices were of the low value item in each pair. Feedback was deterministic, such that choosing this item was rewarded 100% of the time and the alternative choice was never rewarded.

Each trial lasted 5 seconds. At the start of each trial (Figure 2.1B) one of the 10 pairs was presented, one item to the right and the other to

the left of a fixation cross (locations were randomized across trials). The participants had 2.5 seconds to select one of the items using the keyboard. If the participants made a selection within this time window, their choice was confirmed by highlighting the selected item for one second and then the outcome was displayed: either "+10" or "- - -" for one second. During the inter-trial interval a fixation cross was presented in the center of the screen for a variable amount of time until the end of the five seconds. 125 trials were presented per run. Four runs of training were completed for a total of 500 trials (50 presentations of each of the 10 pairs).

Imaging Version. The pairing method for the imaging study was slightly different. Instead of using all 30 pairs, only 15 pairs from the middle portion (822) were used. Three sets of five pairs were created by selecting every third pair starting from 8, 9, and 10, respectively. The three sets of five pairs were train low, "train both," which were used in the training phase and untrained, which were used during the probe phase only. Pair set assignments were randomized across participants. The additional pair type, train both pairs, like the train low pairs, contained one low value and one high value item, but choice of either of these items yielded points during training. We included this pair type to serve as a high-level control in the imaging analysis. The participants were not informed of the fact that there were two pair types during training but were told that some of their choices will earn them points (later converted to real money). In the imaging version, choices were made using an MRI compatible button box. Participants had 1.5 sec to make their

choice once the stimuli were presented (one to the right and one to the left of a central fixation cross, locations randomized across trials). Upon successful choice, the chosen item was highlighted for 500 msec, then the outcome ("+10" or "- - -") was displayed for 500 msec. During the intertrial interval, a fixation cross was presented for a jittered time drawn randomly from an exponential distribution with a mean of 3, truncating values at 1 and 12. Fifty trials (25 train low and 25 train both) were randomly presented per run for a run time of 4 min 45 sec where each pair was presented five times per run. Ten runs of training were completed such that each pair was presented 50 times.

2.2.2.3 Probe

Behavioral Version. Following the completion of training, participants filled in a computer-adapted version of the Barratt Impulsiveness Scale (BIS)-11 questionnaire (Patton et al., 1995). They were then told that they would next perform a new task (Figure 2.1C) where they choose an item in each pair but in this case instead of earning points, a single trial would be drawn at random at the end of the session and their choice on that trial would be honored (i.e., they would receive the item that they had chosen on that trial at the end of the experiment and will stay to consume it in the lab). The pairs from the training task were presented in a random order alongside 10 new Untrained pairs (not presented during training). These pairs also contained high and low value items and were drawn from the same pair matching procedure mentioned above. The task and timing at probe were very similar to that at

training; the only difference is that the outcome (points/no-points) was not displayed following the choice. Trial timing was identical to training omitting the outcome presentation time. Each pair was presented five times during probe and the left-right locations of the items on the screen were randomized across presentations.

Imaging Version. In the imaging version, participants filled in the computer-adapted version of the BIS-11 (Patton et al., 1995) using the MRI-compatible button box prior to the probe phase. At probe, 3 pair types were presented: the 5 Train Low and 5 Train Both pairs from training as well as 5 Untrained pairs. Trial timings were identical to training omitting the outcome (points/no-points) presentation time. Each pair was presented five times during probe and the right-left locations of the items on the screen were randomly assigned across presentations.

2.2.2.4 Questionnaires

As mentioned above, the BIS-11 (Patton et al., 1995) questionnaire was administered between training and probe. At the end of the session, when participants remained in the lab to consume the food item they received, they were also asked to fill in the BIS/BAS (Carver and White, 1994), two questionnaires that assessed the strength of a self-reported personal habit (Ji and Wood, 2007; Verplanken and Orbell, 2003) and were also asked to describe any strategies they used to maximize the number of points during training. The imaging participants also filled out the Kirby et al. (1999) temporal discount-

ing questionnaire.

2.2.3 Behavioral Analysis

Behavioral Version.

Training: We performed a repeated measures logistic regression to test the difference in the odds of choosing the low value to high value item during valid trials from run 1 compared to the following nine runs. To allow comparison across the behavioral and imaging version we divided the entire training session of 500 trials into 10 parts with 50 trials in each part (the 500 trials were presented to participants with 3 short breaks).

Probe: To test if our training was successful in influencing choices, we performed a repeated measures logistic regression to compare the odds of choosing the low value to high value items between the 2 pair types (Train Low and Untrained) during probe. We ran a repeated measures linear regression to look at differences in reaction time (RT) for choices of the low value item between pair types. We also tested for the consistency of choices of the low value items in the two pair types using repeated measures logistic regression: Trained Low and Untrained across the 5 presentations during probe.

Auctions: We calculated the change in WTP of the high and low value items separately between the first and second auction (Δ). We compared that change between the 3 pair types: Train Low (presented during training), Untrained (presented only during probe) and another set that was never presented during either training or probe, using repeated measures linear regression.

Imaging Version.

Training: Similar to the behavioral version we compared the odds of choosing the low value to high value item in each of the pair types for run one compared to the following nine runs to test for learning effects. We also performed a repeated measures logistic regression to compare the odds of choosing the low value to high value item in the Train Low pairs compared to odds of choosing low value to high value items in the Train Both pairs. We used repeated measures linear regression to compare RTs during choices of the low value items between pair types across runs.

Probe: We performed a repeated measures logistic regression to compare the odds of choosing the low value to high value item between the 3 pair types (Train Low, Train Both and Untrained) during probe. We also ran repeated measures linear regression to compare RTs during choices of low value items between the different pair types. Similar to the behavioral version we tested for the consistency of choices of the low value items in the three pair types: Train Low, Train Both and Untrained across the 5 presentations during probe.

We also examined the unique influence on choices during probe of two opposing factors: 1) the number of times the low value items were chosen during training, which represents the influence of extensive training on choice behavior and 2) the difference in WTP between the high and low value item in each pair, which represents the goal-values of the items. For this purpose we performed a repeated measures linear regression to test if the number of

choices of the low value items during training predict participants' choices at probe, while controlling for the difference in WTP between the high and low value items in each pair. We performed this for each pair type (Train Low and Train Both) separately and tested the interaction between pair types.

Auctions: We calculated the change in WTP of the high and low value items separately between the first and second auction (Δ). We compared that change between the 3 pair types: Train Low (presented during training), Train both and Untrained (presented only during probe), using a repeated measures linear regression.

2.2.4 fMRI Acquisition and Analysis

Imaging data were acquired on a 3T Signa Excite MRI scanner (General Electric Medical Systems, Milwaukee, WI) with an eight channel head coil. Functional data were acquired using a T2*-weighted echo planar imaging sequence (repetition time [TR] = 2500 ms, echo time [TE] = 30 ms, flip angle [FA] = 70°, field of view [FOV] = 22 cm^2). Thirty two oblique axial slices with a 3.5 mm inplane resolution were positioned 20° off the anterior commissure-posterior commissure line to reduce the frontal signal dropout (Deichmann et al., 2003) and spaced 3 mm with a 0.5 mm gap to achieve full brain coverage. Slices were acquired in an interleaved fashion and higher order shimming was used to reduce susceptibility artifacts. Each of the training runs consisted of 114 volumes and the probe run consisted of 158 volumes. In addition to functional data, a single 3D T1-weighted high-resolution full brain image ac-

quired using a spoiled gradient recalled pulse sequence (TR = 5.9 ms, TE = 1.2 ms, FA = 11°, FOV = 25 cm^2) was acquired for brain masking and image registration.

Raw imaging data in DICOM format were converted to NIFTI format and preprocessed through a standard preprocessing pipeline using the FSL package (Smith et al., 2004) version 5. Functional image time series were first aligned using the MCFLIRT tool to obtain six motion parameters that correspond to the x/y/z translation and rotation of the brain over time. Second, the skull was removed from the T2* images using the brain extraction tool (BET) and from the high-resolution T1 images using Freesurfer (Ségonne et al., 2004). Spatial smoothing was performed using a Gaussian kernel with a FWHM of 5 mm. Data and design matrix were high-pass filtered using a Gaussian-weighted least-squares straight line fit with a cutoff period of 100 seconds. Grand-mean intensity normalization of each runs entire 4D dataset by a single multiplicative factor was also performed. The functional volumes for each participant and run were registered to the high-resolution T1-weighted structural volume using a boundary-based registration method (Greve and Fischl, 2009) implemented in FSL5 (BBR). The T1-weighted image was then registered to the MNI152 2mm template using a linear registration implemented in FLIRT (12 DOF). These two registration steps were concatenated to obtain a functional-to-standard space registration matrix.

2.2.5 Imaging Analysis

2.2.5.1 Training

The general linear model (GLM) during the training phase included 5 regressors for each pair type: 1) onsets of Train Low trials when low value items were chosen, modeled with a fixed duration of 1 second; 2) onsets of Train Low trials when the low value items were chosen but with actual RTs as duration. We included this regressor to account for specific variability due to RT differences across trials. To improve the interpretation of the first regressor, the RT regressor was orthogonalized with respect to the first regressor so inferences for the first regressor reflect the average BOLD activation during the Train Low trials; 3) onsets of Train Low trials when the low value items were chosen with a fixed duration of 1 second but parametrically modulated by the demeaned number of times the low value item in the pair was chosen during probe. This regressor was added to test whether specific choices during probe could be directly linked to brain changes during training. 4) onsets of Train Low trials when the high value items were chosen with a fixed duration of 1 second; 5) onsets of Train Low trials when the high value items were chosen but with actual RTs as duration orthogonalized with respect to the previous regressor. The same 5 regressors were modeled for Train Both trials. A missed trials regressor was also included. We included the 6 motion regressors described above, framewise displacement (FD) and RMS intensity difference from one volume to the next (DVARS) (Power et al., 2012) as confound regressors. We also modeled out trials with FD and DVARS that exceeded

a threshold of 0.5 by adding a single time point regressor for each "to-be-scrubbed" volume. All regressors were entered at the first level of analysis and all (but the added confound regressors) were convolved with a canonical double-gamma hemodynamic response function. The temporal derivative of each regressor was included in the model. The model was estimated separately for each participant for each run.

Our analysis was aimed at identifying brain regions that showed either increases or decreases with training. Contrasts for the mean BOLD activation for each of Train Low and Train Both choices of low value item trials vs. baseline were estimated for each of the 10 runs separately. The proportion of times that the low value items were chosen within the Train Low and Train Both trials during training was computed for each run within-subject. This proportion tracks individual learning across runs. In a second level, within-subject analysis, the linear relationship between the BOLD contrast and corresponding proportion of low value choices was computed voxelwise for Train Low and Train Both, respectively. Note that an intercept, or column of 1s, was also included in this second level model to account for the overall mean of the data within each voxel. This second level contrast then reflects the within-subject relationship between the BOLD contrast and learning for Train Low and Train Both. At the group level we averaged these values across subjects in two separate one-sample t-tests to obtain the overall learning effect within Train Low and Train Both, respectively. Additionally we used a paired t-test to directly compare the Train Low to Train Both effect. The choices of the low

value items were rewarded for both pair types. However, the participants were not required to choose the low value items to obtain points in the Train Both pairs (since choices of either high or low value items were reinforced). Thus, the paired t-test isolates the process of choosing a low value item that required exertion of self-control (in Train Low pairs) while controlling for response to reward as well as motor and visual processes involved in the choice itself (in Train Both pairs).

Three participants were excluded from the imaging analysis: Two did not choose the low value item in Train Both pairs even once for two of the training runs. The third participant chose the low value items in Train Both runs at exactly the same proportion across all training runs and thus the second level design was rank deficient and not estimable since the regressor for the proportion of low choices was perfectly correlated with the intercept regressor (column of 1s).

We also studied how the BOLD activation related with the proportion of times a low value item was chosen during probe using a parametrically modulated regressor at the first level for Train Low and Train Both trials. For Train Low, this is the third regressor described above. This relationship between the BOLD and later choice during probe was compared between the 10th and first runs and was tested using paired t-tests for Train Low and Train Both, separately. This contrast shows the relationship between training of specific pairs and choices of the same pairs during probe.

2.2.5.2 Psychophysiological Interaction (PPI)

To create the seed for the PPI analysis we defined a 5mm sphere around the dlPFC activation found in the training analysis (see below; MNI coordinate [-52 28 28]) and masked it by the group result. PPI regressors were created by deconvolving the seed to obtain an estimated neural signal using the deconvolution algorithm of SPM (Gitelman et al., 2003), calculating the interaction with the task in the neural domain and then reconvolving to create the final regressor. Following the gPPI modeling procedure of McLaren et al. (2012), three regressors were added to the first level design matrix described above: 1) the raw time course extracted from the seed (after registering the sphere to native space of each run of each participant); 2) A PPI regressor based on onsets of choices of low value items in Train Low pairs; 3) a similar PPI regressor to the previous regressor but for Train Both pairs. We studied the PPI between choices of low value items in Train Low and Train Both pairs within runs 1 and 10 (separately for each run) and between these runs.

2.2.5.3 Probe

We used a GLM for the probe phase which included 4 regressors for each of the three pair types: 1) onsets of Train Low trials when low value items were chosen with fixed duration of 1 second; 2) onsets of Train Low trials when low value items were chosen but with actual RTs as duration. This regressor was orthogonalized with respect to the previous regressor; 3) onsets of Train Low trials when the high value items were chosen with fixed

duration of 1 second; 4) onsets of Train Low trials when the high value items were chosen but with actual RTs as duration, orthogonalized with respect to the previous regressor. To test whether extensive training managed to shift choices from reliance on goal-directed neural mechanisms towards more habitual ones during probe, we included 2 additional regressors to the imaging analysis design matrix: 5) onsets of Train Low trials when low value items were chosen with fixed duration of 1 second and modulation by demeaned proportion of choices of low value items during training; 6) onsets of Train Low trials when low value items were chosen with fixed duration of 1 second and modulation by the difference in WTP between the high and low items in the pair. This was added to test if the difference in WTP had an effect on choices during probe. The last 2 regressors were also added for choices of high value items. The same 8 regressors were modeled for Train Both and Untrained pair type trials (besides the last 4 regressors since the Untrained items were not presented during training). A missed trials regressor was also included. We included confound regressors similar to the ones in the training GLM.

Our analysis was aimed at identifying brain regions showing greater activation during choices of low value over high value items for the Train Low pairs. We also performed comparisons between the Train Low and Train Both pair types for trials where the low value items were chosen. Effects of brain activity greater than baseline were also computed for each of the pair types separately for trials when the low value items were chosen.

All statistical maps for all analyses reported below were corrected at the whole-brain level using a cluster-based Gaussian Random Field correction for multiple comparisons, with an uncorrected cluster-forming threshold of z = 2.3 and corrected extent threshold of $p < 0.05$.

2.3 Results

2.3.1 Behavioral Results

2.3.1.1 Training

Figure 2.3A and 2.3B show the training results for the behavioral and imaging experiments. After 15 (out of 50) repetitions of each pair, the participants learned and continued to choose the low value items for over 80% of the trials for both samples (runs 2 through 10 significantly greater than run 1 p's < 0.01 for the behavioral study and p's < 0.05 except for run 4 $p = 0.058$ for the imaging study). Participants did not choose the low value items significantly more during the subsequent nine runs for the Train Both pairs in the imaging experiment (p's > 0.29 for run 1 compared to runs 2 through 10). In the imaging version participants chose the low value items for the Train Low pairs significantly more than for the Train Both pairs across the entire training task ($p < 0.001$).

Eighty percent of the participants chose the high value item on the first trial. Only by the 10^{th} trial did they reach 50% choice of low value items. Figure 3 presents that data binned by run, which shows that by the end of run 1 they chose the Low Value at 50%, when actually prior to learning that

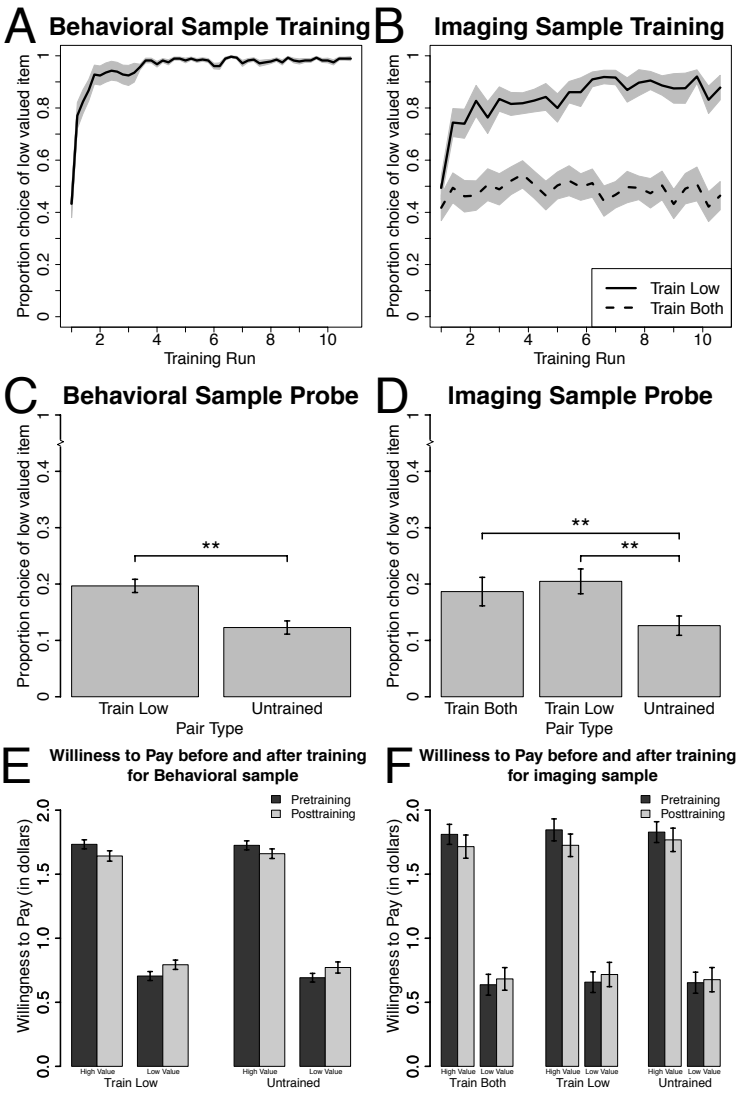

Figure 2.3: *A) Choice of low value items during training for behavioral participants, B) Choice of low value item during training for imaging participants for Train Low and Train Both pair types separately, C) Choices of the low value item during probe for behavioral participants for Train Low and Untrained pairs, D) Choice of the low value item during probe for imaging participants for Train Low, Train Both and Untrained pairs E) Mean WTP pre- and post-training for behavioral participants for Train Low and Untrained pairs, separated by high and low value items F) Mean WTP pre- and post- training for imaging participants for Train Both, Train Low and Untrained pairs, separated by high and low value items. Error bars reflect standard error of the mean.*

choices of the low value items are reinforced, the participants had a very strong preference to choose the higher value items in the pairs.

There were no significant RT differences for choices of low value items between Train Low and Train Both pairs across all runs (p's > 0.3).

2.3.1.2 Probe

The probe was performed on average 3 minutes after the end of training. During probe, participants made choices for later consumption of actual food items to test the effects of training on a preference change. Points/money were not assigned for choices during probe. Figure 2.3D and 2.3C show the results during probe for both samples: participants chose the low value item in the Train Low pairs significantly more often than the low value item in the Untrained pairs: in the behavioral study they chose the low value item on 19.7% of Train Low pair trials versus 12.3% of Untrained trials (Figure 2.3C, $p < 0.001$). Participants in the imaging study similarly chose the low value item on 20.5% of Train Low trials versus 12.6% of Untrained pair trials ($p < 0.001$). In the imaging study, participants chose the low value items in Train Both pair trials 18.7% of the time ($p < 0.001$ compared to choice of low value items in Untrained pair trials; n.s. compared to choices of low value items in Train Low pairs).

In the analysis of persistence of choices of the low value items across the five presentations at probe we found that in the behavioral study there was a main effect of pair type (Train Low vs. Untrained $p = 0.0023$), no main effect of presentation number ($p = 0.85$) and no interaction between presentation number and pair type ($p = 0.82$), suggesting a consistent effect across the five presentations. In the imaging study we found a main effect of pair type (Train Low vs. Untrained $p = 0.01$, Train Both vs. Untrained $p = 0.029$ but no effect of Train Low vs. Train both $p = 0.72$). There was a trending effect of

presentation number ($p = 0.087$), but no pair type by presentation number interaction ($p = 0.6$). Thus the effect was still relatively consistent across the presentations across pair type.

There were no RT differences between choices of low value items in the Train Low and Untrained pair trials in the behavioral study ($p = 0.15$). Similarly, there were no differences in RT during low value choices between Train Both and Train Low pair types in the imaging study ($p = 0.2$), nor between Train Both and Untrained pairs ($p = 0.19$) and between Train Low and Untrained pairs ($p = 0.08$).

2.3.1.3 Auction

The raw WTPs of all pair types in both auctions are presented in Figure 2.3E for the behavioral study and Figure 2.3F for the imaging study. As we ensured in our pairing procedure there were no significant differences in WTP between pair types for either sample (p's > 0.24). There were no significant differences in pre- versus post- training WTP in either study. In the behavioral study we did not find a significant difference in the change in WTP between the two auctions (before and after training) for the Train Low pairs compared to either Untrained or never-seen pairs (p's > 0.4). In the imaging study there was also no significant difference in the change in WTP over time between pair types (Train Both vs. Untrained $p = 0.26$, Train Low vs. Train Both $p = 0.6$ and the one with the largest trend was Train Low vs. Untrained $p = 0.12$). We are not aware of other studies that attempted to show

an effect of training on WTP of items. Careful observation of Figures 2.3E and 2.3F show a regression to the mean of the WTP of the items such that the Higher Value items were rated as less valuable and the Low Value items as more valuable in the 2^{nd} auction compared to the first one.

Furthermore we found that the pairs on which the participants chose the low value items had a lower WTP difference (averages $0.83 and 0.86$ for the behavioral and imaging studies respectively) between the high and low value items compared to the pairs on which they chose the higher value items (averages $1.10 and 1.25$ for the behavioral and imaging studies respectively). There was a main effect of choice (p's < 0.048) but there was no main effect of pair type (p's > 0.15). This result suggests that the training paradigm managed to influence participants' choice behavior during probe primarily on trials when the difference between high and low-valued items was not too large. It should be noted that there was still a highly significant difference in WTP between the low and high items in the pairs where participants chose the low value items at probe even according to the 2^{nd} auction (p's < 0.0001).

In the regression to identify the relative contribution of the number of times an item was chosen during training on how many times it was subsequently chosen during probe and the difference in WTP between the items in each pair, we found that the number of choices of low value items per Train Low pair during training predicted subsequent choices of low value items during probe (p = 0.001). However, the difference in WTP between items in the Train Low pairs did not (p = 0.14). This relationship was not significant for

choices of the low value items in Train Both pairs for either factor. There was no significant interaction between choices of the low value items during training and probe between pair types.

2.3.1.4 Questionnaires

We tested for the correlation between proportion of low value choices on Train Low pairs during probe (indicative of behavioral change) and BIS-11, BIS/BAS, habit strength and temporal discounting. No significant correlations in either sample were found between these measures (all p's > 0.1 without control for multiple comparisons). In the self-report question pertaining to strategies used during training to maximize points, 18 of 28 participants in the behavioral version indicated they chose the item with the lower value. However, in the imaging version, only one participant mentioned this general rule whereas the rest said they had memorized which choices gave them points. Thus, it seems that participants in the behavioral version more easily formed a general rule. This was not the case for participants in the imaging version who formed only specific cue-reward pairings.

2.3.2 Imaging Results

2.3.2.1 Training

The primary analyses studied the linear relationship between BOLD activation during choices of low value items and the proportion of low value item choices in each run across the 10 training runs for Train Low and Train

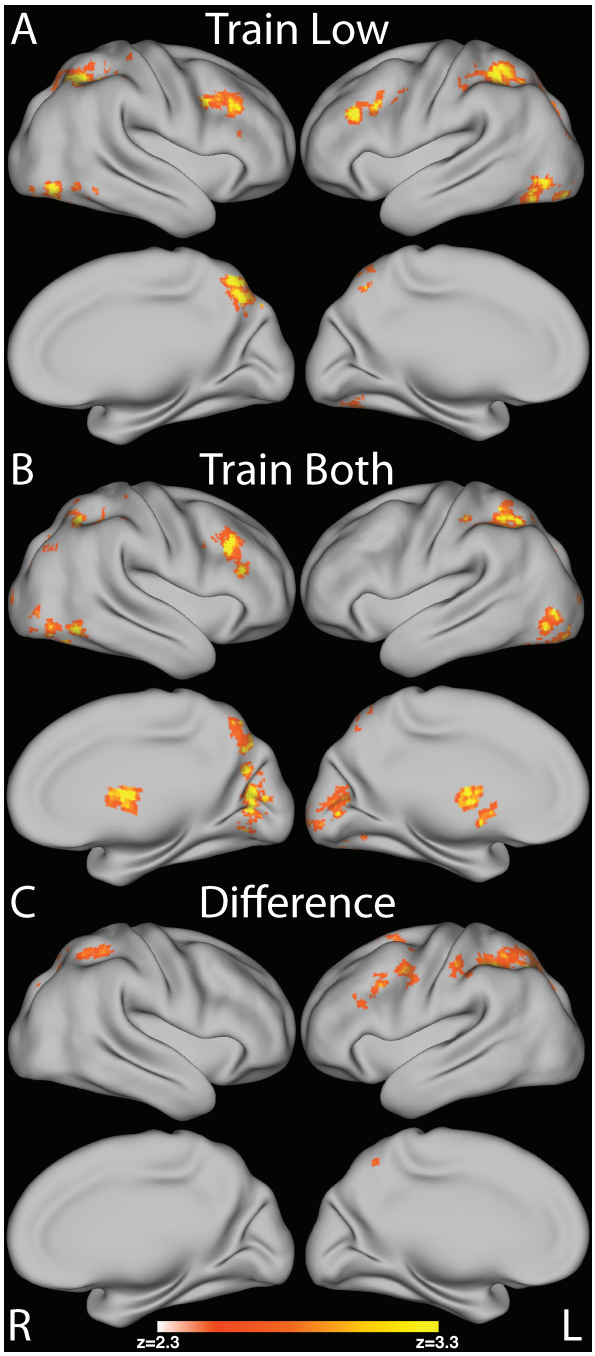

Figure 2.4: *Imaging results showing the negative relationship with proportion of choices of low value items across training run for A) train low pairs and B) train both pairs; C) the difference between these two pair types train both > train low shows a more restricted set of regions including bilateral parietal and only left dlPFC. Subtracting choices of low value items in train both pairs controls for all other trial elements, which do not require self-control because both low value and high value items were reinforced. Surface renderings were created using CARET after mapping of the group statistical maps to an average cortical surface using multifiducial mapping (Van Essen, 2005). All maps are presented at $p < .05$, corrected, as in the accompanying tables.*

Both separately. For Train Low, we found that activity in bilateral dlPFC, parietal cortices and precentral gyrus had a negative relationship with learning (see Figure 2.4A and Table 2.1). A similar result was obtained for the Train Both pairs with low value choices except that there was no negative relationship between the activity in left dlPFC and learning above the correction threshold (see Figure 2.4B and Table 2.2).

Train Low chose Low

Cluster number	Region	# voxels in region	Cluster size	x	y	z	Peak Z
1	L Superior Parietal Lobule	465	3039	12	-66	56	4.23
	R Superior Lateral Occipital Cortex	455					
	L Superior Lateral Occipital Cortex	437					
	R Precuneus Cortex	373					
	R Superior Parietal Lobule	353					
	L Postcentral Gyrus	115					
	R Postcentral Gyrus	102					
	R Angular Gyrus	81					
	R Posterior Supramarginal Gyrus	59					
	L Posterior Supramarginal Gyrus	56					
	L Anterior Supramarginal Gyrus	44					
	L Precuneus Cortex	40					
2	L Inferior Lateral Occipital Cortex	549	1068	-46	-74	-8	3.97
	L Occipital Fusiform Gyrus	210					
	L Temporal Occipital Fusiform Cortex	92					
	L Temporooccipital ITG	37					
3	R Middle Frontal Gyrus	453	713	52	18	32	3.75
	R Precentral Gyrus	52					
	R IFG, pars opercularis	27					
	R IFG, pars triangularis	16					
	R Frontal Pole	15					
4	R Inferior Lateral Occipital Cortex	292	494	42	-68	-16	3.66
	R Inferior Temporal Gyrus	98					
	R Occipital Fusiform Gyrus	28					
	R Temporal Occipital Fusiform Cortex	14					
5	L Middle Frontal Gyrus	265	393	-44	28	28	3.87
	L Precentral Gyrus	37					
	L IFG, pars opercularis	11					
	L IFG, pars triangularis	10					

Table 2.1: *Results from analysis of training-related modulation of activity during choices of low value items on Train Low pairs ($p < .05$, corrected); regions presented here demonstrated negative relationship with the proportion of choices of the low value items on Train Low pairs across the 10 runs. For each cluster, the list shows all regions from the Harvard-Oxford atlas that contained more than 10 voxels within that cluster, along with the peak X/Y/Z location for the cluster in MNI space.*

Train Both Chose Low

Cluster number	Region	# voxels in region	Cluster size	x	y	z	Peak Z
1	R Precuneus Cortex	482	2491	8	-72	10	4.17
	R Intracalcarine Cortex	353					
	L Occipital Pole	273					
	R Superior Lateral Occipital Cortex	250					
	L Intracalcarine Cortex	233					
	R Supracalcarine Cortex	129					
	R Lingual Gyrus	112					
	R Cuneal Cortex	78					
	R Occipital Pole	75					
	R Superior Parietal Lobule	59					
	L Superior Lateral Occipital Cortex	38					
	L Precuneous Cortex	30					
	L Supracalcarine Cortex	25					
	L Lingual Gyrus	20					
	L Cuneal Cortex	15					
2	L Inferior Lateral Occipital Cortex	453	805	-48	-84	-2	3.86
	L Occipital Fusiform Gyrus	130					
	L Temporal Occipital Fusiform Cortex	35					
	L Occipital Pole	15					
	L Lingual Gyrus	10					
3	R Thalamus	112	802	0	-4	14	3.62
	L Thalamus	107					
	L Caudate	67					
	R Caudate	60					
	R Pallidum	22					
	R Putamen	11					
4	R Inferior Lateral Occipital Cortex	397	740	42	-74	-20	3.76
	R Temporooccipital ITG	103					
	R Occipital Pole	65					
	R Occipital Fusiform Gyrus	44					
	R Temporal Occipital Fusiform Cortex	12					
5	L Superior Parietal Lobule	325	726	-30	-56	48	3.56
	L Superior Lateral Occipital Cortex	152					
	L Postcentral Gyrus	85					
	L Posterior Supramarginal Gyrus	36					
	L Anterior Supramarginal Gyrus	22					
6	R Middle Frontal Gyrus	472	712	44	22	30	3.89
	R IFG, pars triangularis	51					
	R Precentral Gyrus	21					
	R IFG, pars opercularis	14					
7	R Superior Parietal Lobule	189	470	36	-52	46	3.49
	R Angular Gyrus	83					
	R Posterior Supramarginal Gyrus	59					
	R Postcentral Gyrus	42					
	R Superior Lateral Occipital Cortex	38					
	R Anterior Supramarginal Gyrus	16					

Table 2.2: *Results from analysis of training-related modulation of activity during choices of low value items for Train Both pairs across the 10 training runs ($p < .05$, corrected); regions listed here demonstrated negative relationship with the proportion of choices of the low value items on Train Both pairs across the 10 runs. For each cluster, the list shows all regions from the Harvard-Oxford atlas that contained more than 10 active voxels within that cluster, along with the peak X/Y/Z location for the cluster in MNI space.*

We suggest that self-control was initially required to overcome the tendency to choose the unreinforced higher valued item in favor of the reinforced

choice of the lower valued item. To test for the unique neural mechanisms underlying choices of low value items in the situation where only the lower valued choice was rewarded and not both, we directly compared the slopes between BOLD and proportion of low value item choices across the 10 runs for Train Low and Train Both using a group level paired t-test. We tested which brain regions had a more positive relationship with the proportion of choices of the low value items in the Train Low pairs across training compared to the Train Both pairs; this controlled for all other processes involved in choice and receipt of reward. We found that the linear relationship between BOLD activation and proportion of choice of low value items was more positive for Train Both than Train Low in bilateral parietal regions and the left dlPFC (see Figure 2.4C and Table 2.3). Previous studies showed differences in the processing of health vs. taste of food items in dieters with different levels of self-control Hare et al. (2009, 2011). As we did not include healthy items in our study nor did we ask participants to consume an item up to satiety (Tricomi et al., 2009) we did not have dieting as an exclusion criterion in this study. After the study, we asked participants to report if they would describe themselves as being on a diet. Four participants reported being on some form of diet (BMI ranging from 22-27). Exclusion of these participants did not change the findings.

No increases in BOLD activation were found as training progressed for choices of the low value items in the Train Low pairs, Train Both pairs or their difference at a whole brain corrected level. In addition, no regions survived a small volume correction of either a 10 mm sphere around the right

Train Both Chose Low > Train Low Chose Low

Cluster number	Region	# voxels in region	Cluster size	x	y	z	Peak Z
1	L Superior Lateral Occipital Cortex	510	1692	-28	-68	34	3.68
	L Superior Parietal Lobule	419					
	L Postcentral Gyrus	199					
	L Anterior Supramarginal Gyrus	156					
	L Posterior Supramarginal Gyrus	90					
	L Precuneous Cortex	27					
2	L Middle Frontal Gyrus	263	687	-46	2	42	3.17
	L Superior Frontal Gyrus	147					
	L Precentral Gyrus	131					
	L IFG, pars triangularis	24					
3	R Superior Lateral Occipital Cortex	214	561	34	-72	44	3.22
	R Superior Parietal Lobule	178					
	R Precuneous Cortex	88					
	R Postcentral Gyrus	17					

Table 2.3: *Results from a whole-brain group paired t-test comparison between choices of low value items for Train Low pairs and choices of low value items for Train Both pairs and their negative relationship with proportion of choices of low value items across the 10 training runs ($p < .05$, corrected). For each cluster, the list shows all regions from the Harvard-Oxford atlas that contained more than 10 active voxels within that cluster, along with the peak X/Y/Z location for the cluster in MNI space.*

dorsolateral putamen coordinate reported by Tricomi et al. (2009) or using the right and/or left putamen masks from the Harvard-Oxford atlas (distributed with FSL). There were also no significant differences in training activation as a function of the number of low value choices at probe for either pair type.

2.3.2.2 PPI

For the choices of the low value items in Train Low greater than Train Both pairs during run 10, we observed a difference in connectivity with the left dlPFC seed region (defined by the training analysis above). This PPI effect was found in parietal and visual regions (see Figure 2.5B and Table 2.4). We

did not observe this PPI effect during run 1. When we tested for the direct comparison between run 10 and run 1 we found greater connectivity with motor regions such as the supplementary motor area and bilateral precentral gyri (see Figure 2.5C and Table 2.5). Thus, it seems that following training, the dlPFC modulated activity in perceptual, attentional and motor regions to facilitate choices of low value items in the Train Low pairs compared to Train Both pairs. When we tested for the separate PPI effects of each condition vs. baseline seed connectivity we found only significant positive PPI effects that might suggest a stronger positive PPI effect of Train Low vs. Train Both with the regions reported above. Based on previous studies we defined a 10 mm sphere around the vmPFC coordinate reported by Hare et al. (2011) to test for a PPI effect with dlPFC. There were no significant PPI effects with this region in any of the analyses reported above.

2.3.2.3 Probe

When participants chose the low value items in either Train Low or Train Both pair types (compared to baseline), we observed an increase in activity in similar regions to those that decreased their activity across training runs (see Table 2.6 and 2.7). Regions showing an increase include visual regions, bilateral parietal regions, anterior cingulate cortex (ACC) (in both pair types) and bilateral dlPFC for Train Both pairs only (see Figure 2.6). Interestingly there were no dlPFC activations while choosing the low value items in the Train Low pairs, but these regions were active during choices of

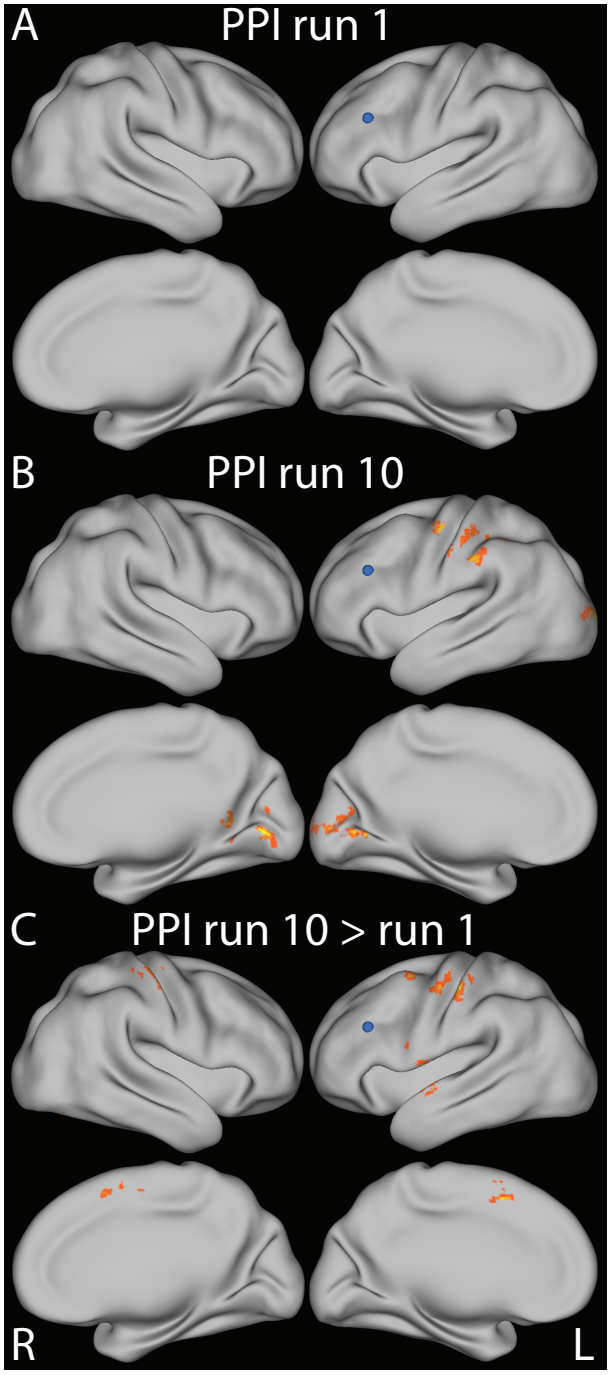

Figure 2.5: *PPI results showing connectivity with dlPFC seed (shown in blue) for choice of low value items in train low pairs versus train both pairs in A) the first run (run 1), B) the last run (run 10) of training, and C) their direct comparison. (All $p < .05$, corrected).*

PPI run 10

Cluster number	Region	# voxels in region	Cluster size	x	y	z	Peak Z
1	L Occipital Pole	194	777	-22	-92	10	3.75
	R Lingual Gyrus	137					
	L Intracalcarine Cortex	119					
	R Intracalcarine Cortex	89					
	L Lingual Gyrus	46					
	R Supracalcarine Cortex	33					
	R Occipital Pole	23					
	L Superior Lateral Occipital Cortex	15					
	L Inferior Lateral Occipital Cortex	10					
2	L Postcentral Gyrus	170	409	-46	-42	44	3.54
	L Anterior Supramarginal Gyrus	124					
	L Posterior Supramarginal Gyrus	50					
	L Precentral Gyrus	43					
	L Superior Parietal Lobule	12					
3	R Inferior Lateral Occipital Cortex	22	135	50	-72	-20	3.31
	R Occipital Fusiform Gyrus	11					
4	R Precuneus Cortex	57	129	16	-50	8	3.26
	R Posterior Cingulate Gyrus	15					
	R Lingual Gyrus	10					

Table 2.4: *Results for PPI analysis showing regions with significant PPI with the left DLPFC seed at run 10 ($p < .05$, corrected). For each cluster, the list shows all regions from the Harvard-Oxford atlas that contained more than 10 active voxels within that cluster, along with the peak X/Y/Z location for the cluster in MNI space.*

low value items in Train Both pairs. This is consistent with a practice-related decrease in the engagement of top-down control systems over choice. However, no regions survived the direct comparison between choices of low value items in Train Low compared to Train Both pairs. Similarly, we did not find any activity above our correction threshold for choices of low value compared to high value items in Train Low pairs. These null findings are likely due to low power resulting from the small number of participants who had choices of the low value items in both is also possible that we did not find differences in the direct comparisons due to the short duration of this phase; Tricomi

PPI run10 > run1

Cluster number	Region	# voxels in region	Cluster size	x	y	z	Peak Z
1	L Postcentral Gyrus	220	585	-52	-18	52	3.23
	L Middle Frontal Gyrus	145					
	L Precentral Gyrus	122					
	L Superior Frontal Gyrus	15					
2	R Postcentral Gyrus	187	306	56	-14	56	3.42
	R Precentral Gyrus	54					
3	R Supplementary Motor Cortex	74	219	-4	8	48	3.11
	R Paracingulate Gyrus	39					
	L Supplementary Motor Cortex	29					
	L Paracingulate Gyrus	28					
	R Superior Frontal Gyrus	24					
4	L Central Opercular Cortex	45	188	-50	-2	12	3.3
	L Precentral Gyrus	40					
	L Anterior Superior Temporal Gyrus	40					
	L Posterior Superior Temporal Gyrus	10					
5	R Inferior Lateral Occipital Cortex	15	145	46	-66	-20	3.41
	R Occipital Fusiform Gyrus	11					

Table 2.5: *Results for PPI analysis showing regions with significant difference in PPI between run 10 and run 1 with the left DLPFC seed ($p < .05$, corrected). For each cluster, the list shows all regions from the Harvard-Oxford atlas that contained more than 10 active voxels within that cluster, along with the peak X/Y/Z location for the cluster in MNI space.*

et al. (2009) did not report any results from the probe phase due to its short duration.

Choices of low value items during probe showed a modulation by choices during training for both pair types in visual, motor and right premotor regions (Figure 2.7A). Further, there was a negative correlation between choices of the low value item during training and activity in the vmPFC and OFC during choices of the low value item for Train Low pairs at probe. We did not find any neural evidence at probe for greater modulation of choices of low value items during training for Train Low greater than Train Both. However, for the contrast of choices of low value items during probe for Train Both greater than

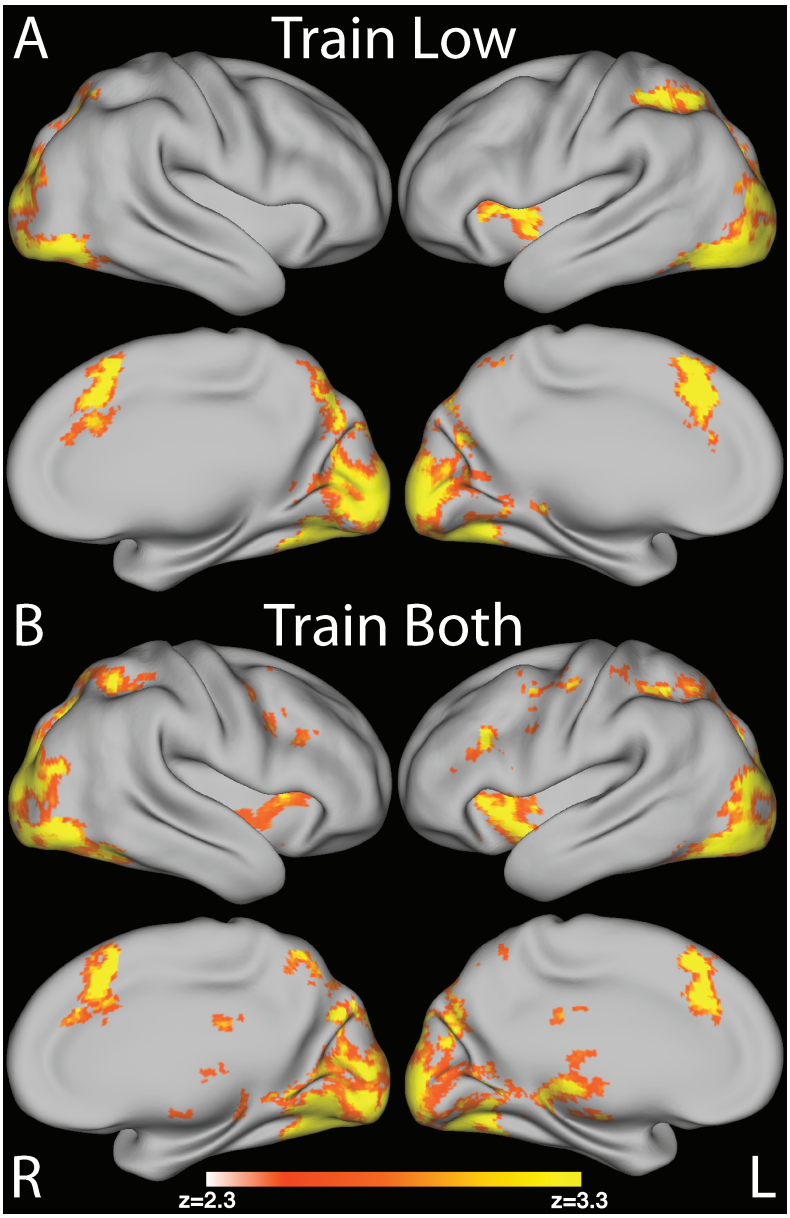

Figure 2.6: *Imaging probe results showing regions exhibiting increased activity with choices of the low value items in the two pair types compared with baseline: A) train low and B) train both ($p < .05$, corrected).*

Probe Train Low Chose Low > baseline

Cluster number	Region	# voxels in region	Cluster size	x	y	z	Peak Z
1	L Occipital Pole	2116	22508	-32	-66	-16	5.78
	R Occipital Pole	2038					
	R Superior Lateral Occipital Cortex	1331					
	L Superior Lateral Occipital Cortex	1188					
	L Inferior Lateral Occipital Cortex	1132					
	R Occipital Fusiform Gyrus	871					
	L Occipital Fusiform Gyrus	843					
	R Inferior Lateral Occipital Cortex	828					
	R Lingual Gyrus	741					
	R Intracalcarine Cortex	700					
	L Lingual Gyrus	534					
	R Precuneous Cortex	516					
	L Intracalcarine Cortex	489					
	L Superior Parietal Lobule	471					
	R Temporal Occipital Fusiform Cortex	355					
	L Temporal Occipital Fusiform Cortex	309					
	L Precuneous Cortex	307					
	R Cuneal Cortex	261					
	Brain-Stem	210					
	L Temporooccipital ITG	166					
	R Supracalcarine Cortex	125					
	L Cuneal Cortex	104					
	R temporooccipital ITG	90					
	L Hippocampus	88					
	R Superior Parietal Lobule	73					
	L Supracalcarine Cortex	32					
	L Thalamus	29					
	L Postcentral Gyrus	25					
2	R Paracingulate Gyrus	508	1786	4	20	52	4.42
	L Paracingulate Gyrus	311					
	R Superior Frontal Gyrus	279					
	L Superior Frontal Gyrus	186					
	R Anterior Cingulate Gyrus	160					
	L Anterior Cingulate Gyrus	98					
3	L Insular Cortex	284	782	-28	12	6	3.94
	L Central Opercular Cortex	75					
	L Putamen	70					
	L Frontal Operculum Cortex	65					
	L Planum Polare	19					

Table 2.6: *Regions showing significant activation for choices of low value items in Train Low pairs greater than baseline during Probe. For each cluster, the list shows all regions from the Harvard-Oxford atlas that contained more than 10 active voxels within that cluster, along with the peak X/Y/Z location for the cluster in MNI space.*

Probe Train Both Chose Low > baseline

Cluster number	Region	# voxels in region	Cluster size	x	y	z	Peak Z
1	R Occipital Pole	2227	28611	30	-74	-8	5.58
	L Occipital Pole	2084					
	R Superior Lateral Occipital Cortex	1658					
	R Lingual Gyrus	1226					
	L Superior Lateral Occipital Cortex	1166					
	L Inferior Lateral Occipital Cortex	1125					
	R Inferior Lateral Occipital Cortex	1107					
	R Occipital Fusiform Gyrus	879					
	L Occipital Fusiform Gyrus	790					
	L Lingual Gyrus	757					
	R Intracalcarine Cortex	673					
	L Thalamus	595					
	R Precuneus Cortex	530					
	L Insular Cortex	472					
	L Intracalcarine Cortex	444					
	R Temporal Occipital Fusiform Cortex	442					
	R Cuneal Cortex	414					
	L Superior Parietal Lobule	399					
	L Temporal Occipital Fusiform Cortex	348					
	R Superior Parietal Lobule	346					
	L Cuneal Cortex	330					
	L Putamen	318					
	L Precuneus Cortex	269					
	R Temporooccipital ITG	192					
	Brain-Stem	186					
	R Thalamus	181					
	L Frontal Operculum Cortex	157					
	L Middle Frontal Gyrus	141					
	L Pallidum	138					
	R Supracalcarine Cortex	133					
	L Temporooccipital ITG	127					
	L Hippocampus	114					
	L Central Opercular Cortex	106					
	L IFG, pars opercularis	85					
	L Postcentral Gyrus	81					
	R Hippocampus	65					
	L IFG, pars triangularis	37					
	L Planum Polare	35					
	L Temporal Pole	24					
	L Posterior Temporal Fusiform Cortex	22					
	L Supracalcarine Cortex	22					
2	R Paracingulate Gyrus	382	1475	2	22	50	4.31
	L Paracingulate Gyrus	298					
	R Superior Frontal Gyrus	246					
	L Superior Frontal Gyrus	140					
	R Anterior Cingulate Gyrus	77					
	L Anterior Cingulate Gyrus	74					
3	R Putamen	110	625	18	10	2	3.52
	R Caudate	76					
	R Frontal Orbital Cortex	12					
4	R Insular Cortex	218	455	44	12	2	3.5
	R Frontal Operculum Cortex	146					
	R Central Opercular Cortex	59					
5	L Precentral Gyrus	154	319	-44	-12	50	3.32
	L Middle Frontal Gyrus	97					
	L Postcentral Gyrus	36					
6	R Middle Frontal Gyrus	111	232	48	10	56	3.41
	R Precentral Gyrus	42					
7	R Precentral Gyrus	50	103	46	10	32	3.19
	R Middle Frontal Gyrus	30					
8	R Middle Frontal Gyrus	46	85	46	20	24	2.95
	R IFG, pars opercularis	12					
9	R Posterior Cingulate Gyrus	44	80	6	-28	28	2.96
	L Posterior Cingulate Gyrus	31					

Table 2.7: *Regions showing significant activation for choices of low value items in Train Both pairs greater than baseline during Probe. For each cluster, the list shows all regions from the Harvard-Oxford atlas that contained more than 20 active voxels within that cluster, along with the peak X/Y/Z location for the cluster in MNI space.*

Train Low pairs, we found greater activity in vmPFC and OFC (Figure 2.7B and Table 2.8). This result is consistent with a shift from goal-directed to habitual responding (and decreased reliance on goal-values) during probe, but only for the Train Low pairs. This result was obtained with only n=12 during probe (that had choices of low value items in both pair types) so should be regarded with caution.

Train Both > Train Low

Cluster number	Region	# voxels in region	Cluster size	x	y	z	Peak Z
1	L Frontal Pole	202	343	-24	58	-6	3.48
	L Frontal Medial Cortex	36					
2	L Posterior Inferior Temporal Gyrus	33	216	-44	-10	-34	3.33
	L Anterior Middle Temporal Gyrus	27					
	L Temporal Pole	22					
	L Anterior Inferior Temporal Gyrus	19					
	L Posterior Temporal Fusiform Cortex	19					
3	R Posterior Inferior Temporal Gyrus	82	155	44	-14	-36	3.57
	R Posterior Temporal Fusiform Cortex	24					
	R Anterior Inferior Temporal Gyrus	12					

Table 2.8: *Regions showing significant activations at probe for the contrast of modulation by choices of Low Value Items during training for Train Both Greater than Train Low Pairs. For each cluster, the list shows all regions from the HarvardOxford atlas that contained more than 10 active voxels within that cluster, along with the peak x/y/z location for the cluster in MNI space.*

2.4 Discussion

The ability to influence food choices is critical to solving health-related problems currently affecting large portions of the U.S. and world population (World Health Organization, 2012). Here, we report the results of a new behavioral paradigm, which enhanced the likelihood of choosing a less-preferred food for actual consumption over a previously more-favored food. In this task, pairs of appetitive junk food items were presented during a training period of

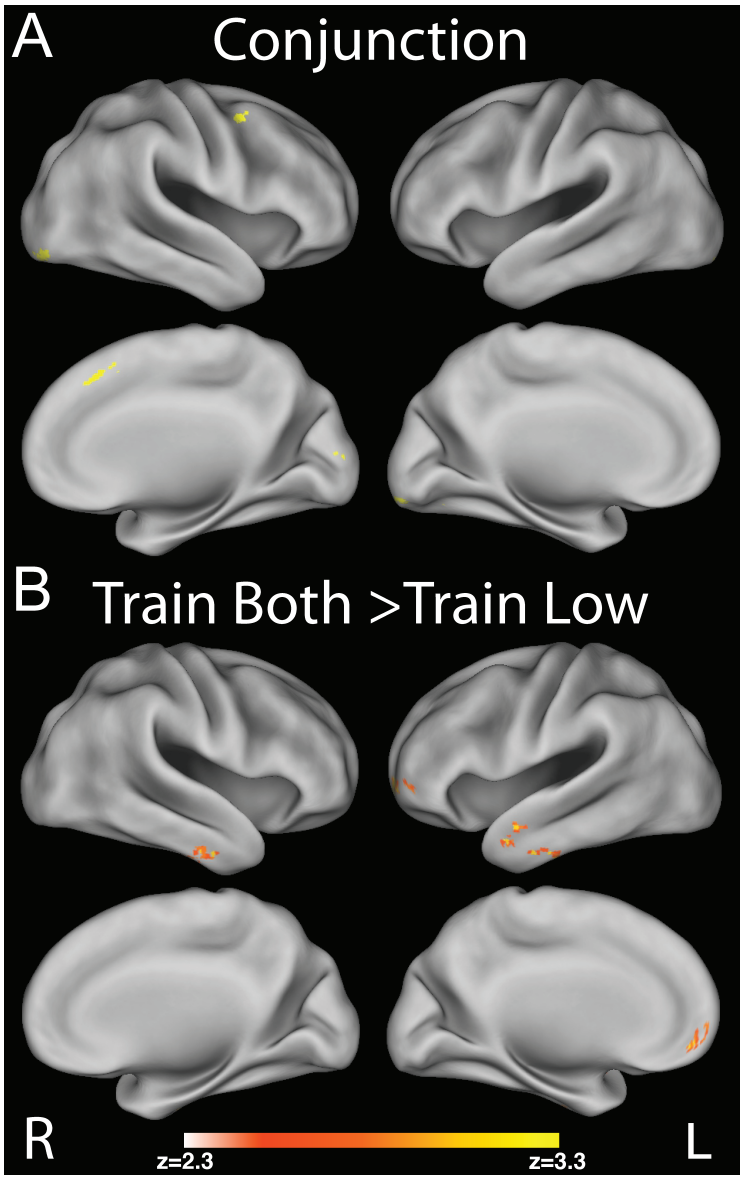

Figure 2.7: *Imaging probe results showing regions exhibiting A) the conjunction of positive modulation by choices during training for both pair types and B) the contrast of modulation by choices of low value items during training for train both greater than train low pairs ($p < .05$, corrected).*

1 hr, such that each pair contained a lower value item versus a higher value one; in the critical condition, only choices of the lower value item were reinforced with money. In a subsequent probe phase, where participants made choices for later actual consumption, they chose the previously reinforced lower value items significantly more than similar value items in untrained pairs. We replicated the behavioral results in an independent sample of healthy participants, scanned with fMRI while performing the task. We found that, as extensive training progressed, activity in regions in the brain that are part of the cognitive-control network (the dlPFC and bilateral parietal cortices) had a negative linear relationship associated with choosing the lower value item. Furthermore, we found that this pattern of activity was specific to the left dlPFC and bilateral parietal cortex only for choices of the lower value items that required exertion of self-control (while controlling for all other choice-related processes including receipt of reward).

Recent studies reported effective dietary interventions using incentives (Driver and Hensrud, 2013; Volpp et al., 2008). Our study provides a clue of mechanistic insight into the potential effectiveness of such a program. Furthermore, it might suggest that repeating the procedure we performed here could prove helpful to obtain long-term effects via reduction of engagement of self-control mechanisms.

These results align with and extend current findings in the neuroeconomics literature. Hare et al. found that a similar region of left dlPFC was more active in dieters with greater self-control (Hare et al., 2009) and also

in healthy participants (Hare et al., 2011) when focusing on the health rather than on the taste aspects of food. Our results extend those findings to a choice situation, showing that, in healthy participants, this same region of left dlPFC (alongside parietal regions, also reported by those studies) decreases its activity with extended training of choosing a less-preferred item. With repeated choices, the self-control network was less and less necessary to choose the lower value items over the higher value ones. Figner et al. (2010) used rTMS in a temporal discounting task to show that disrupting activity of the left but not right dlPFC led to choices of smallershorter options over largerlater ones. The authors concluded that this region serves a role in self-control in the domain of temporal discounting. On the basis of Dosenbach et al. (2007), we suggest that the regions we found here to decrease their activity with extensive training are part of the frontoparietal network that is involved in active adaptive control, in particular, adjusting the exertion of topdown control in response to feedback. It should be highlighted that, although the choices for the low value items in the training phase were not made for consumption, choosing them still required participants to override their initial preference for higher value items in each pair, to achieve a different goal of monetary reward, and thus required exertion of self-control. It is plausible that the decrease in these regions stems from facilitation resulting from extensive training. However, we believe that the fact that there were no RT differences between pair types and between the beginning and end of training suggests that the neural effect we observed goes beyond a simple facilitation effect.

During the probe phase, we found that activity in a similar network of self-control regions increased when participants chose low value items in each of the pairs for later consumption (see Figure 6). There was great overlap, especially in parietal regions, with brain regions that decreased activity as training progressed. Thus, this network that once decreased activity with training is now activated during choice of low value items in the absence of out- come, suggesting that the values of these items were not changed enough and that exertion of self-control was still required to choose them. It is possible that prolonged training will "detach" the involvement of these regions when choosing low value items during probe.

We identified significant modulation of connectivity of the left dlPFC ROI between pair types, consistent with previous studies (Hare et al., 2009, 2011). During the last run, there was greater connectivity for choices of low value items in the train low over train both pairs with parietal and visual regions suggesting a potential topdown process (Corbetta and Shulman, 2002, 2011). Furthermore, in the comparison between run 10 and run 1, there was greater connectivity for choices of low value items in train low pairs over the same choices in train both pairs with primary motor regions and SMA. This might be related to spillover of urges into the motor cortex (Gupta and Aron, 2011) and/or the action competition in motor cortex (Klein-Flügge and Bestmann, 2012). These results, together with the probe results, might hint at ongoing changes during training that could have led to a more substantial preference change had we used a longer training session.

We had hypothesized that we will observe a shift from goal-directed to more "habitual-like" responding following extensive training. However, we did not identify any regions that increased their activity with the progression of extensive training, particularly the striatal regions predicted on the basis of the animal literature (Yin et al., 2004) and previous human fMRI studies (Wunderlich et al., 2012; Tricomi et al., 2009). There are several possible reasons why we did not replicate these previous imaging results. Most importantly, both of those studies involved longer training across several days. In addition, the Tricomi et al. (2009) study involved repeated pressing of a button to obtain a reward, rather than a choice between two options, which might have led to the putamen response because of its involvement in motor processes. In the Wunderlich et al. (2012) study, participants repeated the choices across 3 days, and those choices were between two abstract options rather than food items. We claim that the participants in our study did not treat the items as abstract stimuli. This is apparent from their posttask reports and the fact that, on 80% of the initial trials, they chose the higher valued items. Thus, it is possible that it requires more training to form habitual responding for items that contain inherent values. Nevertheless, the connectivity results suggest that the extensive training shifted responding more toward a stimulusresponse representation over a goal-directed one. Furthermore, choices of the low valued items during training predicted lower activity in vmPFC for train low and not train both pair trials during probe (while accounting for the difference in WTP between the items in each pair) lending credence to the idea that extensive

training leads to a stronger goal-directed-to-habitual shift (but only to the low value items in train low pairs.)

We did not find a change in valuation of the items between the two auctions. We are not aware of any other study that reported a change in bids in such an auction following a behavioral manipulation. We did observe an interesting significant regression to the mean between the two auctions. We do not have the tools in this study to conclude whether this would occur naturally without the training procedure between the auctions. It is possible that this occluded our ability to find a significant valuation difference that would have followed the choice preference change induced by training.

The low value items in the train both pairs were chosen during probe slightly less frequently (but not significantly) than the low value items in the train low pairs. It is reasonable to assume that even the partial reinforcement of these items led to greater choice during probe compared with untrained pairs. The self-report posttask questionnaires of the imaging version suggests that the inclusion of the train both pairs made it harder for the participants to form a rule for the task and thus led to increased variance in their choices of the low value items for the train both pairs. This in turn might have led to increased choices of the low value items during probe. We can speculate that, in a longer training paradigm, these pairs would have shown a smaller effect than the train low pairs com- pared with untrained pairs. Furthermore, the fact that participants showed a consistent effect of choices at probe across the five repetitions but did not show a strong choice preference for the low

value items overall in either pair type speaks against a demand characteristic explanation of the probe results.

Our study still leaves several open questions to be addressed in future studies. First, can this enhancement of choices be applied to the case of healthy over unhealthy food items and not only within junk food snacks? We believe it is plausible given that healthy items such as fruit and vegetables usually obtain positive values, although lower than nonhealthy snacks. Second, the training and probe were done on specific pairs. Therefore, one might ask if the change of value will be generalized beyond the specific pairs? The finding that the effect at probe was found on pairs with smaller (although still highly significant) WTP difference leads us to believe that our task could have been much more successful if aimed to influence preference of items with closer WTP with prolonged and/or repeated training. Furthermore, even changing choices in fixed pairs can be ecologically valid to enhance a specific choice one faces on an everyday basis, for example, choosing carrots over chips as an evening snack. Finally, an interesting question is how long lasting the effect will be and how maintenance can be modulated by the nature and length of training. The finding that choices persisted during the five presentations of pairs at probe shows that, at least during this short period, the choices were consistent. Only a study involving a larger delay will show if this was consolidated into longer-term memory. One additional potential caveat for the face value of our procedure is the limited choice window of 1.5 sec during probe, which does not apply to real-world choices. That is the case for many laboratory studies,

but we can report that participants missed less than 1% of trials overall in the probe phase in both studies (with an average RT of less than 1 sec), which suggests that they had enough time to make this decision. Tasks that include an ad libitum consumption phase at the end of an experiment allow testing the influence of laboratory tasks on real-world food consumption. However, usually this does not allow for testing how preferences changed on more than two items.

The significance of this study is twofold: First, we show that an extensive training session lasting only 1 hr can shift participants' preferences for later food consumption. Compared with untrained pairs, we managed to enhance participants? choices of less-valued items by almost 10% via only 1 hr of training. As far as we know, our study is the first to show an ability to influence choice preferences for food items in humans. Second, we show that preference change is associated with a decrease in activity of self-control regions previously implicated in focusing on long-term goals in decision making in the con- text of food health over taste (Hare et al., 2009, 2011) and/ or intertemporal discounting (Figner et al., 2010; McClure et al., 2004). This suggests that reinforced practice at making better choices may be a potential mechanism to engrain these choices and thus lead to better dietary choices in real-world settings.

Chapter 3

Memory Interference

3.1 Introduction

When retrieved, established memories enter a labile state that renders them susceptible to modification, providing an opportunity to strengthen, weaken or update memories. These memories then re-stabilize through a process known as reconsolidation in order to persist (Nader et al., 2000). Reconsolidation has been shown to be protein-sythesis dependent and transient. Amnestic agents such as anisomycin applied at least ten minutes, but no more than six hours after memory retrieval blocked the return of fear (Duvarci and Nader, 2004). Memory updating during reconsolidation has been demonstrated in many species using several different memory paradigms, suggesting that this process is a fundamental feature that spans different kinds of memory (see Besnard et al., 2012; Alberini and Ledoux, 2013; Reichelt and Lee, 2013, for review).

Important potential clinical applications for memory updating during reconsolidation have been proposed, for example in the treatment of post-traumatic stress disorder (PTSD, Debiec and Ledoux, 2006; Brunet et al., 2008). Patients with PTSD who were given the beta-adrenergic blocker pro-

pranolol shortly after being asked to describe the traumatic event they had experienced showed a marked decrease in physiological responding during traumatic script-driven imagery one week later (Brunet et al., 2011). Non-invasive behavioral retrieval-extinction of fear within the reconsolidation window has also been shown to be effective in the return of fear following Pavlovian cued fear conditioning (Monfils et al., 2009; Schiller et al., 2010).

Although there have been several successful efforts to interfere with memories during reconsolidation in order to prevent the return of fear, relatively few have focused on updating appetitive behavior. These efforts have mostly focused on appetitive Pavlovian conditioning such as drug use (Milton et al., 2008; Lee and Everitt, 2008a). Administration of propranolol had a limited effect on the treatment of drug addiction (Milton et al., 2012). However, retrieval-extinction manipulations have proven useful for reducing conditioned place preference for morphine and cocaine in rats as well as cue-induced heroin craving in humans (Xue et al., 2012). Behavioral interference with a memory within the reconsolidation window could prove useful for updating maladaptive behavior in favor of improved behavior. Many of the successful efforts to update maladaptive memories however have targeted Pavlovian rather than instrumental memories.

Exton-McGuinness et al. (2014) have shown that well-learned instrumental memories can be disrupted by administration of a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist in rats. Previous studies have failed to demonstrate disruption of instrumental memories during recon-

solidation (Hernandez and Kelley, 2004; Mierzejewski et al., 2009), but the discrepancies in the findings are likely due to differences in the parameters during the reactivation session necessary to destabilize the memory (Piñeyro et al., 2014). Censor et al. (2014) recently showed that procedural memory in humans is susceptible to updating when applying repetitive transcranial magnetic stimulation (rTMS). Fewer studies have employed a behavioral retrieval-extinction paradigm during reconsolidation to target procedural memories for updating.

Walker et al. (2003) trained human participants on a motor sequence task and 24 hours later trained the participants on a new motor sequence immediately after brief rehearsal of the sequence from the previous day. They found that speed and accuracy for the day 1 sequence decreased as a result of the interference of the second motor sequence training when the latter was performed immediately, but not when performed six hours after the reminder. However, to our knowledge, no study has targeted memories for contingencies that govern choice behavior for updating using a behavioral retrieval-extinction paradigm.

In this study, we employ an ABA renewal paradigm where training is first conducted in context A, reversal learning is conducted in context B, then an extinction test is conducted in context A to test whether reversal learning within the reconsolidation window reduces renewal of the first-learned response. This approach has clear implications for lasting behavioral change.

3.2 Materials and Methods

3.2.1 Participants

70 healthy participants completed two memory interference studies. Participants were placed into one of two experimental conditions. They started reversal training on day 2 either 10 min or 6 hr after a reminder of day 1 training stimuli (for details please see below section 3.2.2.2). Table 3.1 summarizes participant demographic details for the two studies. Sample sizes are similar to previously published studies.

Study	Group	N	Gender (F/M)	Age (Mean ± SD)	p (age)	
3.1	10min	17	12/5	20.5 ± 2.5	0.3	0.9
	6hr	19	7/12	21.3 ± 2.3		
3.2	10min	16	11/5	20.5 ± 2.5	0.4	
	6hr	18	14/4	21.4 ± 3.1		

Table 3.1: *Demographic details for memory interference studies in chapter 3. P values reflect significance in two-sided independent samples t-tests for age. SD (Standard Deviation).*

All participants were right handed, had normal or corrected-to-normal vision, no history of psychiatric or neurologic disease and were not taking any medication that would interfere with the experiment. Participants agreed to participate in the study over three consecutive days and gave informed consent. The study was approved by the institutional review board (IRB) at the University of Texas at Austin.

3.2.2 Task

Participants agreed to come in for four study sessions at two locations over three consecutive days in two memory interference studies. Figure 3.1 outlines the design for studies 3.1 and 3.2. All details were identical for both studies, except for the number of stimuli and the number of times each stimulus was repeated. These differences are summarized in Table 3.2.

Study	# of stimuli	# of times each stimulus was presented on day 1	# of times each stimulus was presented on day 2
3.1	8	10	5
3.2	4	8	4

Table 3.2: *Differences in the number of stimuli and the number of times each stimulus was presented during the day 1 and day 2 training phases of memory interference studies.*

3.2.2.1 Train day 1

On the first visit, participants learned to press one of two buttons to earn points 80% rather than 20% of the time in context A. This was in room A in building A and the computer screen background color was A. Half the stimuli were associated with a more favorable right button press and the other half with a left button press. Stimuli were black and white photographs of neutral objects. The number of stimuli and the number of times each stimulus was repeated are summarized in Table 3.2. Stimuli appeared in random order per block of eight or four presentations so that the time between presentations

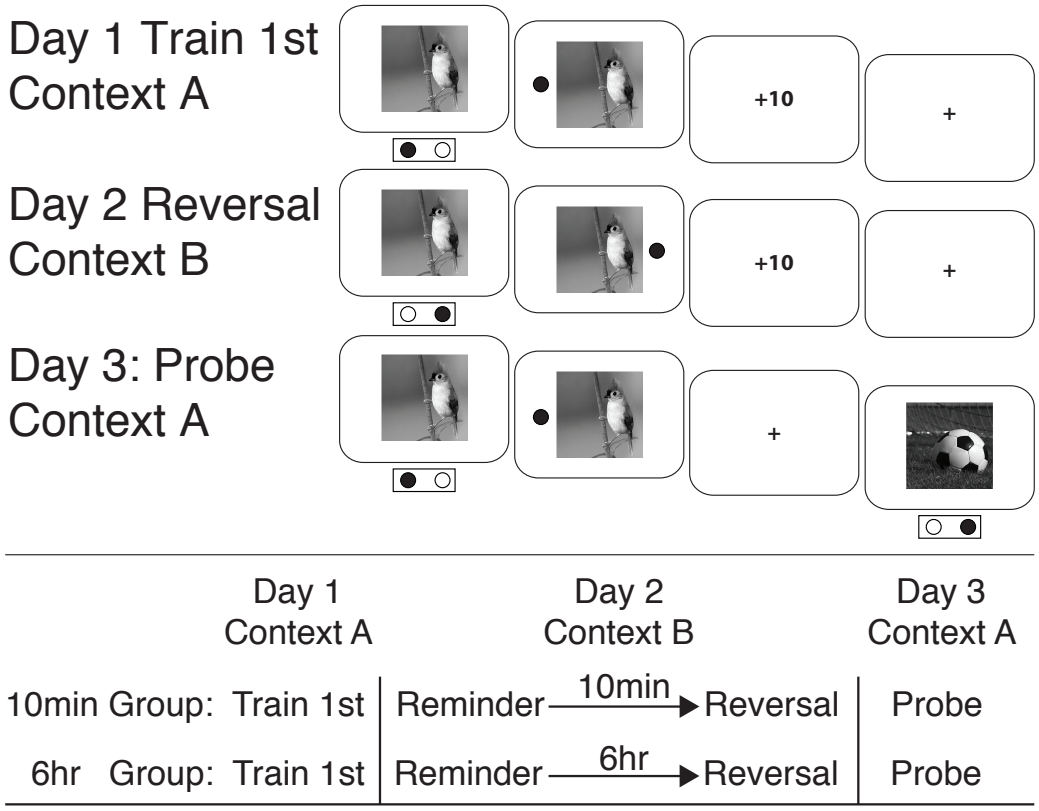

Figure 3.1: *Schematic of experimental procedure for memory interference studies. Details of each step are described in section 3.2.2. Briefly, participants learn to press one of two buttons to earn points 80% vs. 20% of the time on day 1 in context A (room A in building A). On day 2, contingencies are reversed in a new context B (room B in building B) either ten minutes or six hours after reminder. On day 3, participants perform a probe under extinction conditions in context A.*

of a particular stimulus remained relatively constant.

3.2.2.2 Reversal day 2

On the second visit, participants went to a different room in a different building (context B) and filled out a computer adapted version of BIS-11

(Patton et al., 1995) then were reminded of the stimuli with a single exposure to each of the stimuli. To ensure that the participants were attending to the stimuli, they were asked to press a different button (the space bar) when a stimulus appeared on the screen. Participants were assigned to one of two groups. One group received the reminder six hours before reversal training on the second day and the other ten minutes before reversal training on the second day. These times were shown to correspond to times outside and within the reconsolidation window respectively (Duvarci and Nader, 2004; Monfils et al., 2009). During training on the second day, the first day contingencies were switched and participants learned to reverse what they had learned the previous day. Each stimulus appeared five times for study 3.1 and four times for study 3.2 during reversal training on day 2. We chose to reduce the training by half from day 1 during reversal training on day 2 to avoid overtraining effects during reversal since participants learn faster during reversal learning compared to initial leaning (pilot data not shown). We aimed for learning on day 1 and day 2 to be equivalent.

3.2.2.3 Probe day 3

On the third day, participants returned to room A in building A that they had visited on day 1 (context A). They were presented with the same items as the previous two days and asked to press one of two buttons, but no outcome was provided. Participants were told that although they would receive no outcome information, the computer would continue to count points

in the background and that it was important for them to press the button they thought would yield points. Renewal was measured as choices consistent with first-learned contingencies on day 1. This ABA renewal paradigm was designed to detect updating of contingency memory trace when training after a contingency switch occurs within the reconsolidation window (i.e. ten minutes after a reminder).

3.2.3 Analysis

3.2.3.1 Training

To test for successful training to press one button over another for each stimulus, we ran repeated measures logistic regression on the odds of choosing the high-reward response (that yields points 80% of the time) to the low-reward response (that yields points 20% of the time) on the last block vs. the first block of presentations during training on day 1 with a grouping factor for participant. We ran the same regression model for reversal training on day 2. We also ran regression to compare the groups (10min/6hr) on the last block of presentations on each day to test for any differences in learning between the groups.

3.2.3.2 Probe

We performed a repeated measures logistic regression on the odds of choosing the high-reward response from day 1 to the high-reward response from day 2 against equal odds with a participant grouping factor separately for the

10min and 6hr groups. These regressions test for renewal of the first-learned behavior (high-reward response on day 1) during probe on day 3 (which takes part in context A, the same as training on day 1). We also ran a repeated measures logistic regression to test for the difference between the 10min and 6hr groups on the odds of performing the first-learned to second-learned behavior. We hypothesized that the 6hr group (i.e. those who received reversal training outside the reconsolidation window) would exhibit significant renewal compared to the 10min group (i.e. those whose reversal training occurred within the reconsolidation window and whose memory for first-learned contingencies were targeted for updating by contingencies on day 2).

The influence of successful training on day 1 on renewal and its interaction with group assignment were tested using linear regression. We hypothesized that the influence of training from day 1 on renewal would be weaker for the 10min group compared to the 6hr group, which would suggest that the memory for contingencies from day 1 was updated by contingencies from day 2 in the 10min group.

3.3 Results

3.3.1 Training

Participants learned to choose the high-reward option (button press associated with 80% reward) by the end of training on day 1 and learned to switch their responses on day 2 (Figure 3.2A and C and Table 3.3). There were no differences in choice of high-reward option between the 6hr and 10min

groups on the last block of presentations on either day or in either study, suggesting that learning was equivalent between the groups on both days. There were also no differences in reaction time during training between the groups (p's > 0.15).

Study	Day	Group	Prop.	O.R.	95% C.I.	p (time)	p (group)
3.1	Day 1	10min	78%	5.2	[2.83 9.58]	< 0.0001	0.9
		6hr	79%	5.63	[3.16 10.04]	< 0.0001	
	Day 2	10min	73%	3.90	[2.02 7.56]	0.0001	0.7
		6hr	69%	3.20	[1.67 6.11]	0.0004	
3.2	Day 1	10min	73%	4.18	[1.96 8.91]	0.0002	0.8
		6hr	73%	3.19	[2.02 5.01]	< 0.0001	
	Day 2	10min	71%	3.79	[1.71 8.43]	0.001	0.6
		6hr	67%	2.63	[1.46 4.73]	0.001	

Table 3.3: *Descriptive statistics for training phase behavior in memory interference studies. Proportion (Prop.) choice of high-reward option at the end of training on each day. Odds ratio (O.R) for choice of high- to low-reward option at the end of training on each day. Confidence interval (C.I) on odds ratio and p-value (time) for odds of choosing high-reward option at the end of training vs. the beginning of training and p-value (group) for the odds of choosing high- to low-reward option at the end of training between groups.*

3.3.2 Probe

Using eight stimuli (study 3.1), participants in the 6hr group displayed significant renewal of the first-learned response (mean proportion choice of first-learned = 63%, odds of first- to second-learned response p = 0.002). However, renewal of first-learned behavior was not mitigated by reversal learning within the reconsolidation window (mean proportion choice of first-learned =

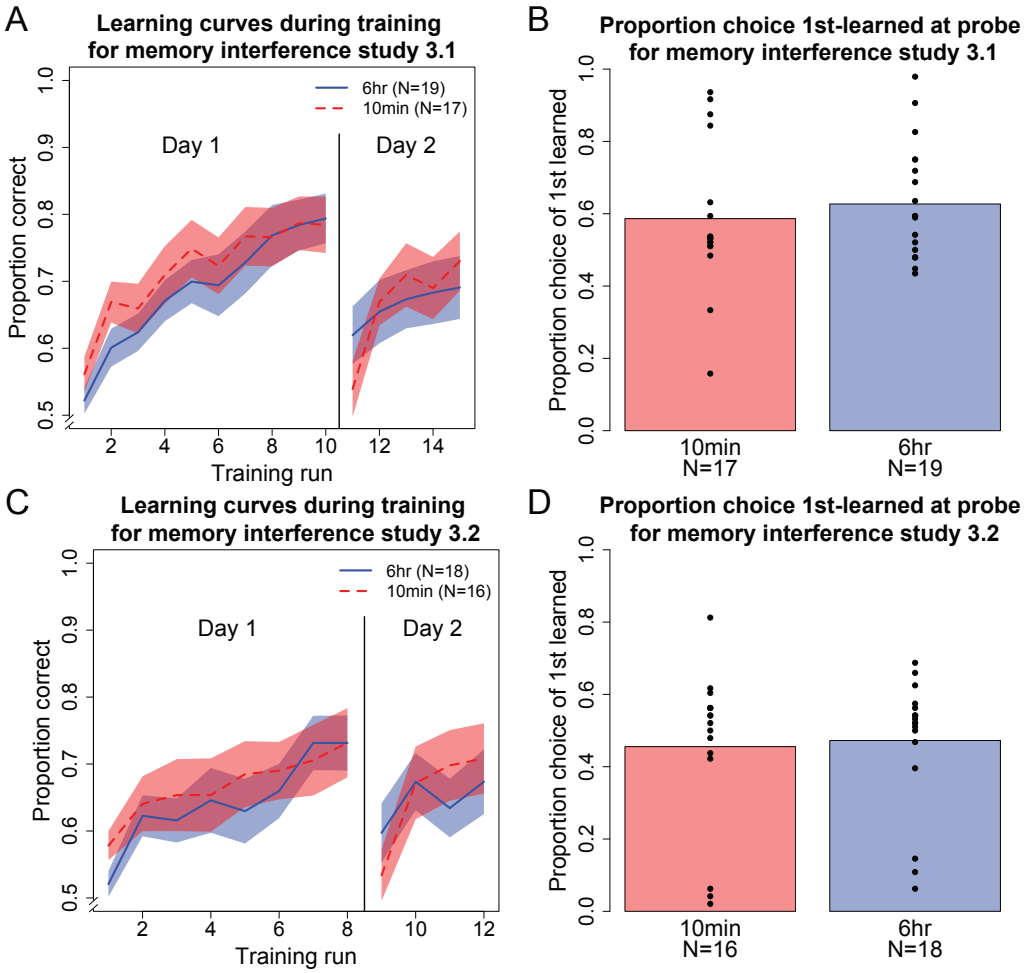

Figure 3.2: *Behavioral results for memory interference studies. The top row (A,B) shows results from study 3.1. Participants were trained on eight stimuli (N = 36). The bottom row (C,D) shows results from study 3.2. Participants were trained on four stimuli (N = 34). A,C) The solid blue line represents the mean proportion of correct responses (defined as a high-reward response yielding points 80% of the time) over runs of the task for the 6hr group. The interrupted red line shows the same for the 10min group (group Ns in legend on top right). The shaded area represents one standard error of the mean (SEM). B,D) The bars represent the mean proportion of first-learned response (high-reward response from day 1) during the probe phase under extinction conditions. The left red bar includes participants in the 10min group, the right blue bar includes participants in the 6hr group. The dots represent the proportion of first-learned responses for each individual participant.*

59%, odds of choosing first- to second-learned in 10min group p = 0.074, and p = 0.57 for the comparison of 6hr to 10min group, Figure 3.2B). Simplifying the task and using four stimuli did not achieve the hypothesized reduced renewal effect in the 10min group in a second sample of N = 34 (study 3.2, mean proportion choice of first-learned = 45% vs. 47% for 6hr group, odds of choosing first- over second-learned for 10min vs. 6hr group p = 0.7, Figure 3.2D). There were no differences in reaction time between the groups at probe (p's > 0.9).

We also tested the the effect of learning on day 1 on renewal of first-learned behavior at probe on day 3. There was a main effect of correct choices at the end of day 1 on renewal of responses at probe (p = 0.0008 for study 3.1 and 0.05 for study 3.2), no main effect of group assignment (10min/6hr, p's > 0.5) and no interaction between responses at the end of day 1 and group assignment on choice at probe (p's > 0.8), suggesting that there was not significant interference with memory for contingencies from day 1 by conducting reversal learning during the reconsolidation window.

3.4 Discussion

Targeting specific memories for updating during reconsolidation is a promising avenue for treating disorders such as PTSD and drug abuse. In the studies described in this chapter, our goal was to interfere with appetitive memory for choice contingencies using reversal learning within the reconsolidation window. We employed an ABA renewal paradigm to test renewal of

first-learned responses under extinction conditions after conducting reversal learning either within the reconsolidation window (ten minutes after a reminder of the stimuli) or outside the reconsolidation window (six hours after the reminder). We found that although there is some evidence of significant renewal of first-learned responses when reversal learning was conducted outside the reconsolidation window, there was no evidence of significant updating of memory for first-learned responses or attenuation of renewal of first-learned responses following reversal learning within the reconsolidation window.

Piñeyro et al. (2014) showed that reactivation duration of a fear memory is a critical factor for trace destabilization. More specifically, they found that four minutes, but not one minute of reactivation before the extinction of a fear memory prevented the return of fear. In our studies, reactivation consisted of a single one second presentation of each of the stimuli, which amounted to a maximum of 32 seconds of reactivation. The short reactivation task might not have been sufficient to initiate synaptic protein degradation, which typically takes place at least three minutes after retrieval and is crucial for the destabilization of retrieved memories (Lee et al., 2008).

In our studies, the reminder also involved a different response (press space-bar) than on day 1 training (press one of two buttons for a chance to earn points). Lee and Everitt (2008b) trained rats to associate a lever press with a sucrose reward. Rats were then administered the NMDAR antagonist MK-801 on the second day after a reminder of day 1 training. Reactivation of the lever press-sucrose association was achieved through re-exposure that was

either contingent or not on a lever press. Reconsolidation of the lever press-sucrose memory was blocked for rats that received the reminder contingently, but not those who received the reminder noncontingently upon a lever press. The authors concluded that stimuli may have to be presented in the same manner as during training in order to render previously acquired memories unstable. Not performing the same task as on day 1 for the reminder in our studies could have contributed to weaker destabilization of the memory for day 1 contingencies and thus a lack of memory updating during reversal learning.

Spatial context has also been suggested to play an important role in the updating of episodic memories. Hupbach et al. (2008) showed that new learning in the same spatial context as original learning is necessary and sufficient for the incorporation of new information into existing episodic memories. In our studies, the reminder and by design the reversal learning were conducted in a different spatial context than learning on day 1. The switch in spatial context during the reminder on day 2 may have contributed to a lack of full reinstatement and destabilization of the memory for day 1 contingencies in our studies. However, there is evidence that reconsolidation is not triggered when no new information is learned during the reminder trial (Sevenster et al., 2012). Thus it is possible that reminder trials that are identical to the previous day training trials might not provide any new information. In our studies, performing a different response during the reminder trials than on the previous day's training trials might not provide any new information in the form of a prediction error to trigger reconsolidation. The lack of prediction errors

during reminder in our studies might also be a factor in the lack of updating of day 1 contingency memory traces.

Further studies that vary the retrieval task, timing and spatial context during reminder should be conducted to determine the retrieval parameters necessary to destabilize memory for contingencies in the present task, and render it amenable to updating by new contingencies. Although recent years have seen an exponentially growing body of evidence demonstrating reconsolidation of human memories across memory domains (Besnard et al., 2012), not all of the precise boundary conditions that govern reconsolidation across types of memory have been identified and characterized. In a recent review, Schwabe et al. (2014) pose a number of questions for the scientific community to answer relating to human memory reconsolidation. These questions pertain to potential individual differences in the susceptibility to memory updating after retrieval and factors that might influence such differences, the duration of the reconsolidation window and the time over which any memory modifications might last, and the brain mechanisms that support reconsolidation of various types of memory. Although many questions remain to be answered, a better understanding of memory reconsolidation processes has high potential for the treatment of certain psychological and behavioral disorders.

Chapter 4

Trained Inhibition

4.1 Introduction

Inhibition is a fundamental function of cognition. Deficits in inhibitory control can be very disruptive in everyday life and lead to drug abuse, problem gambling and/or attention deficit hyperactivity disorder (ADHD, see Bari and Robbins, 2013, for a recent review). In the laboratory, inhibitory control is most often studied using a motor response inhibition paradigm such as the go/nogo or stop-signal tasks. For the stop-signal task, participants press a button in response to stimuli presented on the screen (Go trials). On a small subset of trials an unexpected stop-signal appears (Stop trials). This usually takes the form of a tone, but it can be a visual stop-signal. The stop-signal appears some variable time after the stimulus appears, i.e. a stop-signal delay (SSD). Participants must inhibit the prepotent motor response when the stop-signal appears.

Verbruggen and Logan (2008) showed that response inhibition is not always a "top-down" process. Consistently associating the stop-signal with specific stimuli during stop-signal training produced an automatic "bottom-up" inhibitory process. The right inferior frontal gyrus (rIFG) has been impli-

cated in response inhibition and thought to send a top-down signal to initiate stopping in the presence of stop cues (Aron and Poldrack, 2006; Aron et al., 2003; Chambers et al., 2006). Furthermore, the rIFG is also activated in the absence of stop cues for faces that had previously been consistently associated with a stop-signal (Lenartowicz et al., 2011). Training inhibition could prove to be a useful tool to elicit automatic inhibitory signals mediated by rIFG to avoid action in the service of lasting behavioral change.

Whereas in chapter 3 we attempted to update memory traces for a response, in the present chapter we are reporting on efforts to strengthen the inhibition of an older behavior in order to weaken it. Veling et al. (2013b) observed a reduction in the choice of unhealthy palatable foods that were associated with a stop-signal during training, in favor of foods not associated with a stop-signal in healthy young adults, using an adaptation of the Go/NoGo task. Additionally, Wessel et al. (in press) showed that associating particular neutral shape stimuli with a stop-signal that required participants to rapidly inhibit a prepotent response resulted in lower subjective value placed on those items in a subsequent auction, as compared to neutral stimuli that had not been associated to a stop-signal. The researchers ensured that the main result was due to stopping action rather than aversiveness, effort, conflict, or salience associated with stop-signals. Taken together, these results suggest that associating a stop-signal not only with inherently valuable stimuli such as food, but also with neutral stimuli, decreases the subjective value placed on specific stimuli associated with the stop-signal compared to others that were

not associated with the stop-signal.

In the studies presented in this chapter, we adapted an automated response inhibition version of the stop-signal task (Verbruggen and Logan, 2008), as well as a simpler Go/NoGo task, seeking to elicit an automatic inhibition process during choice between junk food options. We hypothesized that food items previously paired with a stop-signal during a training phase would lead to less frequent choice of those items in favor of items that were not associated with the stop-signal in three cue-avoidance studies.

4.2 Materials and Methods

4.2.1 Participants

93 healthy participants completed three cue-avoidance studies. Table 4.1 summarizes participant demographic details for the three studies. Studies 4.1 and 4.2 correspond to studies 5 and 6 in Schonberg et al. (2014a). Sample sizes are similar to other previously published studies.

Study	N	Age (Mean ± SD)	Gender (F/M)	BMI (Mean ± SD)
4.1	42	21.3 ± 2.5	30/12	23.3 ± 6.2
4.2	26	18.9 ± 1.2	22/4	22.7 ± 3.4
4.3	25	20.4 ± 2.0	16/9	22.6 ± 3.2

Table 4.1: *Demographic details for cue-avoidance studies in chapter 4. SD (Standard Deviation). BMI (Body Mass Index).*

All participants had normal or corrected-to-normal vision, no history

of psychiatric, neurologic or metabolic illness, no history of eating disorders, no food restrictions and were not taking any medication that would interfere with the experiment. Participants were informed that the goal of the experiment was to study food preferences and were asked to refrain from eating or drinking anything but water for four hours prior to their visit to the laboratory (Plassmann et al., 2007). All participants gave informed consent. The study was approved by the institutional review board (IRB) at the University of Texas at Austin.

4.2.2 Task

4.2.2.1 Auction

First, participants were endowed with $3 and took part in an auction where they bid on 60 appetitive junk food items. This auction procedure provided us a measure of willingness to pay (WTP) that reveals each participant's preference for these items (Becker et al., 1964; Plassmann et al., 2007, Figure 2.1A). Details on the auction procedure can be found in section 2.2.2.1.

4.2.2.2 Item selection

Items were rank ordered based on WTP, so that item #1 had the highest WTP value and #60 the lowest. The eight items with rank orders 8-15 were designated as higher-value and the eight items with rank orders 46-53 were designated as lower-valued items. Items were then assigned to one of four training conditions: 1) four items high-value Go, 2) four items high-value

Stop, 3) four items low-value Go and 4) four items low-value Stop (Figure 4.1). This selection procedure ensured pairing of high-value Stop with high-value Go items and low-value Stop with low-value Go items, so that two items in a pair had similar WTPs. These pairs of items with similar WTP were later presented during a probe phase (see below). It was expected that participants would, a priori, be indifferent about choosing between the two items based on stated pre-experimental preferences.

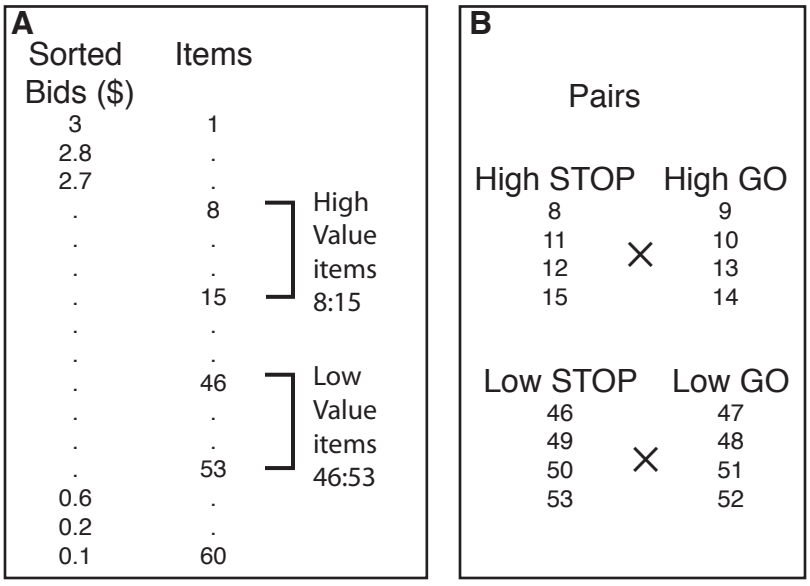

Figure 4.1: *Sorting and pair matching procedure used for studies in chapter 4. A) Items are rank ordered based on bid obtained in the auction (Figure 2.1A). Items are classified into high value (8:15) and low value items (46:53). B) High and low value items were assigned to one of two training conditions (Stop, associated with a stop-signal and Go, not associated with a stop-signal). Item Stop/Go condition assignments were counterbalanced across participants.*

In order to ensure 25% cue frequency (as is common in stop-signal

tasks, Logan and Cowan, 1984), we chose an additional four high-value items (out of items ranked 16-23) and four low-value items (out of items ranked 38-45) to be associated with the Stop cue. They were later used to form pairs during probe, made up of high-value Stop and low-value Stop items. A fourth pair type during probe was made up of high-value Go and low-value Go items. High-value items were chosen much more often than low-value items, as expected, and thus results from those comparisons are neither shown nor discussed.

4.2.2.3 Training

Study 4.1 & 4.2 During training, participants were instructed to press a button on the keyboard as quickly as possible every time a food item stimulus appeared on the screen (Go trial), unless they heard a neutral tone (Stop trial, Figure 4.2A). They were instructed to refrain from pressing the button (stop) when they heard the tone. Items appeared on the screen one at a time in random order and remained on the screen for a fixed duration of one second followed by an inter-trial interval lasting on average three seconds, with a range of one to twelve seconds. Stop items were consistently associated with the stop cue. The tone initially sounded 250 ms after the food item appeared on the screen (i.e. stop-signal delay [SSD]) and if the participant failed to stop, the tone sounded 50 ms sooner on the next Stop trial, making it easier to stop. If the participant successfully stopped, the tone sounded 17 ms later on the next Stop trial, making it slightly more difficult to stop in time. This staircase

procedure ensured that the participants successfully stopped in about 75% of Stop trials without being able to predict onset of the tone, as would be the case if we used a fixed SSD.

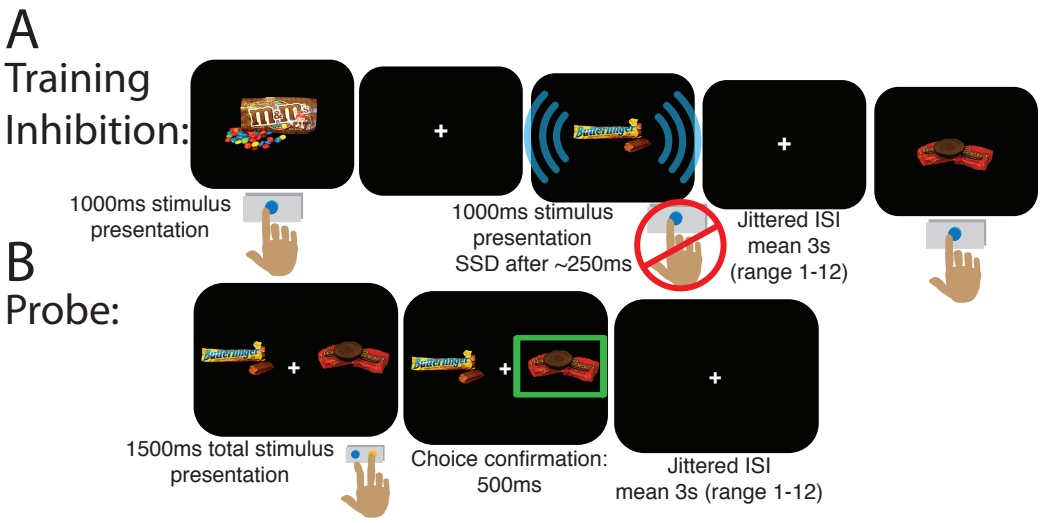

Figure 4.2: *After an initial auction, A) participants were asked to press a button as quickly as possible when they saw a food item on the screen (Go item)* except *when they heard an infrequent tone (Stop items). The tone sounded at a variable time after the food stimulus appears on the screen (stop-signal delay [SSD]). SSDs were adjusted using a staircase procedure. Participants were told to withhold their response when they heard a tone. B) During the later probe phase, two images of food items appeared on the screen. For pairs of interest, WTP for the two items was similar. Pair assignments are outlined in Figures 4.1. Participants were told that a single trial would be selected at random at the end of the experiment and that their choice on that trial would be honored, meaning they would receive the food item they chose in that particular trial*

Study 4.3 In this study, the stop-signal was visual rather than auditory. A red octagon appeared in the background at the same time the food image

stimulus appeared on the screen, with no SSD. This very salient shape acted as the stop cue and signaled to the participant to withhold his or her response. This modification of the task using a visual stop cue was adopted in order to increase stop success. Studies 4.1 & 4.2 were designed to ensure only 75% success, which might lead to a weak automatic inhibition process to stop items. All other aspects of this task aside from the stop cue form (visual rather than auditory) and the timing of the stop cue appearance (immediately rather than after SSD) were identical to those used for studies 4.1 & 4.2.

4.2.2.4 Probe

After training, participants filled out a computer adapted version of the BIS-11 questionnaire (Patton et al., 1995). About four minutes after the end of cue-avoidance training, they were told to choose between two items that appeared on the screen in a probe phase (Figure 4.2B). They were told that a single trial would be chosen at random at the end of the experiment and that their choice on that trial would be honored, meaning that they would receive the item they had chose on that trial at the end of the experiment. At trial onset, the two items in a pair were presented directly to the right and left of a central fixation cross. Participants had to make their choice within 1.5 seconds, using one of two buttons on the keyboard that corresponded to the left and right items. The chosen item was then highlighted with a green rectangle drawn around it for 500 ms. After choice confirmation, a sole central fixation cross appeared on the screen during the inter-trial interval, which lasted on

average three seconds, with a range of one to twelve seconds. If the participant did not make a choice within 1.5 seconds, a message would appear on the screen asking them to please choose faster, followed by the inter-trial fixation cross and the next trial. Pairs during probe were made up of 64 unique pairs made up of: 1) four high-value Go vs. four high-value Stop items (16 unique pairs), 2) four low-value Go vs. four low-value Stop items, 3) four high-value Go vs. four low-value Go and 4) four high-value Stop vs. four low-value Stop items (Figure 4.1). Each unique pair was presented twice during probe. The order of left-right screen location assignment was randomized across presentations and across participants.

4.2.2.5 Questionnaires

At the end of the experiment, participants took part in a second auction identical to the first. After a random auction trial was played out and choice on a random probe trial was honored, participants remained in the lab to consume any food they won and fill out questionnaires online. These questionnaires are described in section 2.2.2.4.

4.2.3 Analysis

4.2.3.1 Probe

We hypothesized that cue-avoidance training would induce a preference change, reflected in more frequent choice of Go items (i.e. successful avoidance of Stop items). To test for the shift in preference, we performed

repeated-measures logistic regression implemented in the "lmer" function included in the "lme4" library in R (de Boeck and Wilson, 2004) to compare the odds of choosing Go to Stop items against equal odds. We ran the regression separately for high- and low-value pairs. To test for differences in reaction time (RT) during choices of Go and Stop items, we ran repeated-measures linear regression for high- and low-value pair trials separately.

4.2.3.2 Auction

To look at any change in the subjective value placed on individual items due to cue-avoidance training, we used repeated-measures linear regression to test the two-way interaction between time (pre- and post-training auctions) and training condition (Go and Stop) on WTP, separately for high-value and low-value items. This interaction tests whether the change in WTP over time is different for Go and NoGo items. P values for the effects in the mixed models were calculated using the Kenward-Roger approximation for degrees of freedom (Kenward and Roger, 1997).

Because the items were chosen so that their WTPs were on relative extremes of the WTP distribution, we saw regression to the mean between the first and the second auctions, with WTPs for high-value items going down and WTPs for low-value items going up. In order to better account for regression to the mean, we looked at the main effect of factor Go/Stop item assignment as well as its interaction with value (high-value versus low-value items) on WTP at the second, post-training auction, while accounting for WTP on the first,

pre-training auction using repeated-measures linear regression with a grouping factor for participants.

We also investigated the influence of the change in WTP from pre- to post- training auctions on the number of times a particular item was chosen by Go/NoGo item assignment (separately for high- and low-value items) using repeated-measures linear regression with a grouping factor for participants.

4.3 Results

Participants in Study 4.2 were significantly younger than in the other two samples (p's < 0.003), but none of the samples differed on self reported Body Mass Index (BMI, p's > 0.5).

We varied the length of training after the initial study (study 4.1, which included 12 repetitions of all 60 snack food items), in order to test whether more repetition (16 repetitions, study 4.2) would have a different effect on choice. Additionally, in a bid to increase stop success, we eliminated the SSD and employed a salient visual stop cue (study 4.3). We hypothesized that increased stop success during training would have a stronger effect on choice during probe.

4.3.1 Probe

Although stop success was significantly higher in study 4.3 than in the other two samples (91% vs. 64%, $p < 0.0001$), we found no differences in choices of Go and Stop items (Figure 4.3A, with all statistics detailed in

Table 4.2). Additionally, there were no differences in RT between choices of Go and Stop items (all pairwise p's > 0.07).

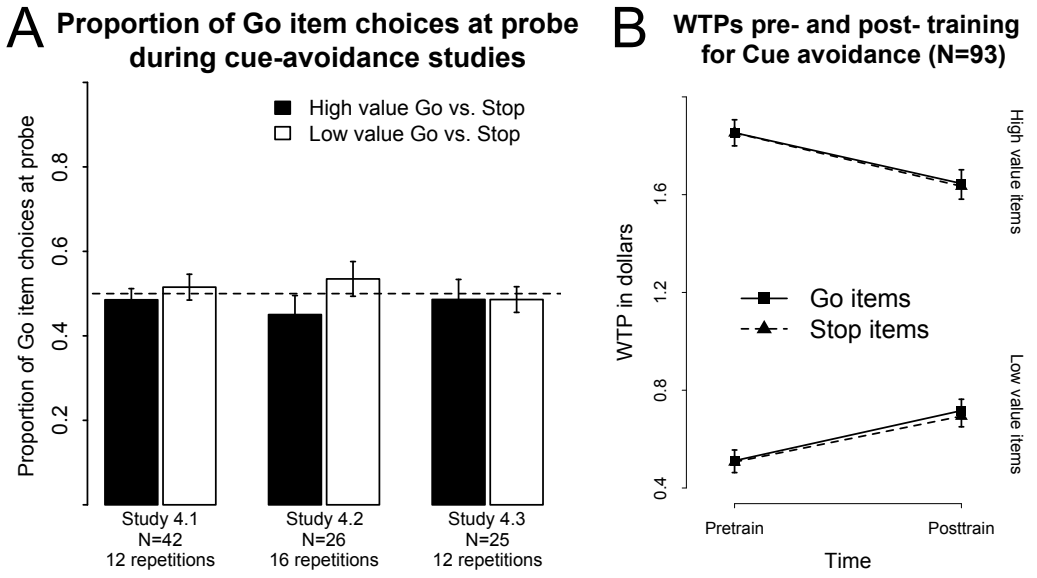

Figure 4.3: *Behavioral results for cue-avoidance studies (Studies 4.1 and 4.2 also found in Schonberg et al., 2014a). A) Proportion choice of the Go item in pairs of high-value Go vs. Stop (black) and low-value Go vs. Stop (white) for three cue-avoidance studies. All p's non significant for odds of choosing Go over Stop item in repeated-measures logistic regression. B) WTP before and after training for Go and Stop items separately in pairs of high-value Go versus high-value Stop pairs (top) and low-value Go versus low-value Stop pairs (bottom). The sample includes all participants from studies 4.1, 4.2 and 4.3. No significant interaction for time by item type (Go or Stop) in a repeated-measures linear regression. All error bars reflect one standard error of the mean (SEM).*

As mentioned above, we repeated the auction after probe to look at the effect of cue avoidance training on the subjective value placed on items across all participants in the cue avoidance studies (N = 93). Mirroring the

Study	Pair Type	Proportion	Odds Ratio	95% C.I.	p
4.1	HV Go v Stop	49%	0.95	[0.74 1.16]	0.5
	LV Go v Stop	52%	1.06	[0.81 1.4]	0.7
4.2	HV Go v Stop	45%	0.79	[0.5 1.23]	0.3
	LV Go v Stop	53%	1.16	[0.8 1.68]	0.4
4.3	HV Go v Stop	49%	0.93	[0.6 1.45]	0.7
	LV Go v Stop	49%	0.95	[0.74 1.22]	0.7
All Studies	HV Go v Stop	48%	0.89	[0.73 1.08]	0.2
	LV Go v Stop	51%	1.05	[0.89 1.25]	0.5

Table 4.2: *Descriptive statistics for probe phase behavior in trained inhibition studies. Proportion choice of Go over Stop items for high-value (HV) and low-value (LV) pairs separately. Odds ratio (O.R) for choice of Go to Stop item. 95% Confidence interval (C.I.) on odds ratio and p-value for odds of choosing Go to Stop item.*

lack of choice effect, there were no differential effects in WTP over time for Go and Stop items, meaning high-value Go and Stop items decreased in value and low-value Go and Stop items increased in value equally (Figure 4.3B, interaction between time [pre-/post-training] and item assignment [Go/Stop] on WTP were non-significant, p's > 0.6). In order to better account for regression to the mean, we ran a mixed model for the effect of item assignment (Go / Stop) and its interaction with value-level assignment (high-/low-value) on WTP at the second auction accounting for WTP at the first auction with a grouping factor for participants. Item assignment had no impact on WTP in this analysis (main effect $p = 0.6$) and no interaction with value-level assignment (interaction term $p = 0.9$). Cue avoidance training does not appear to have influenced the subjective valuation of Go and Stop items differentially.

Finally, the influence of the change in WTP pre- to post-training (WTPΔ

[WTP2 - WTP1]) on the number of times a particular item was chosen at probe as a function of item assignment (Go/Stop) across all cue-avoidance studies (N = 93) for high-value items revealed a main effect for WTPΔ ($p < 0.0001$) and a main effect for item assignment ($p = 0.01$), but no interaction ($p = 0.2$). For low-value items, there was a main effect of WTPΔ ($p < 0.0001$), but no main effect of item assignment ($p = 0.7$) or interaction with WTPΔ ($p = 0.2$) on number of times an item was chosen at probe. Better retention of original value in the high-value items and higher valuation of low-value items after cue avoidance training appears to be related to choice behavior, but this relationship does not differ for Go and Stop items. Additionally, participants took part in the second auction after they completed the choice probe phase. Previous research has shown that choice influences value (Brehm, 1956; Sharot et al., 2009), thus it is possible that choices during probe account solely for less regression to the mean on WTP for high-value and more regression to the mean for low-value items.

4.4 Discussion

Training inhibition to avoid certain foods is an appealing prospect for tackling the obesity epidemic. Indeed, many individuals have trouble regulating food intake, often despite a strong commitment to maintaining or losing weight (e.g. Klesges et al., 1992). This could in part be due to the fact that eating behavior can take on impulsive characteristics (Hofmann et al., 2008; Hall, 2012). Thus, finding ways to decrease impulsive eating is of particular

interest.

Veling et al. (2013a) influenced participants' valuation and choices of palatable foods. Participants chose food items previously associated with a stop-signal less often in favor of items that were not associated with a stop-signal. This choice reduction was shown to be modulated by a decrease in valuation for items associated with a stop-signal. We were not able to replicate these findings in the three studies presented in this chapter. Significant differences between our study design and the Veling studies might explain the lack of significant results in the current studies.

First, Veling et al. (2013a) used pictures of seven snack foods on their own, outside of their packaging, that had previously been rated as palatable by an independent group of participants (Veling et al., 2013b). In our studies, 60 snack food items pictured with their packaging (Plassmann et al., 2007) were used. The influence of repeated advertising of the products used in our studies may have played a role in preventing the effectiveness of cue-avoidance training, although our sorting and item selection procedure based on participants' subjective valuation of all items makes it unlikely that prior advertising would have affected Go and Stop items differentially. Associating stop-signals with neutral stimuli (stimuli that do not have inherent value) reduces their valuation at auction (Wessel et al., in press). These results lend further credence to the low likelihood that advertising played a significant role in preventing replication by boosting the value of food items used in the present studies. Furthermore, evidence from other studies in the lab show

that a reduced stimulus set during cue-approach training (the mirror of the cue-avoidance task, discussed in chapter 5) can amplify choice effects at probe (Schonberg et al., 2014a). Additional studies would have to be conducted to investigate the effect of reducing the stimulus set during cue-avoidance training on choice at probe.

Second, Veling et al. (2013a) consistently associated a stop-signal with half of their stimuli during the Go/NoGo task whereas we associated the stop-signal with 25% of our stimuli during cue-avoidance training. We chose 25% as the proportion of all trials to be Stop trials to be consistent with previous stop-signal studies (Verbruggen and Logan, 2008; Logan, 1994). Keeping Stop trials relatively rare ensures that Go (in this case pressing a button as quickly as possible) is a prepotent response that must be inhibited when the Stop-signal appears. The effect of increasing the proportion of trials that are Stop trials has not been systematically investigated. Further studies would have to be conducted to determine whether a larger proportion of Stop trials during cue-avoidance training would influence choice at probe.

Third, Veling et al. (2013a) presented the Stop cue immediately after the food item disappeared from the screen, did not emphasize speed of responding and provided feedback on each trial whereas we presented the Stop cue along with the food stimulus either a variable time after or at the same time the food stimulus appeared. Additionally, we did not provide trial-by-trial response accuracy feedback. Because participants were required to maintain information about the stimulus during the response window in the Veling

studies (since they received feedback on their responses after the stimulus disappeared), the association between food stimulus and stop-signal was repeatedly reinforced. It is likely that this formed a direct stimulus-stop goal association. In our studies, SSD was on average 250 ms in studies 4.1 and 4.2 and 0 ms in study 4.3. Although the food stimulus remained on the screen for a fixed one second, it became behaviorally irrelevant after the stop-signal appeared. Thus encoding of the food stimulus might have been weaker. We also did not provide trial-by-trial feedback, which might have led to a weak food stimulus-stop-signal association. The latter might not have been retrieved consistently during choice at probe, leading to weak avoidance of Stop items when choosing.

Participants in the Veling et al. (2013a) did not have a time limit within which to make their choice and were not aware of the consequences of their choice. We presented each of the Go and Stop items eight times in all, twice in each of 16 unique pairs, during the choice probe phase. Each choice had to be made within 1.5 seconds and participants were explicitly told that a single trial would be drawn at random and honored, meaning they would receive the item they chose on that particular trial. Although 1.5 seconds is enough time for a participant to make a choice (confirmed by the low proportion of missed trials at probe), choices had to be made quickly and perceived choice regret for a particular item could have influenced their choice on the next trial where that item was presented again, especially since participants were choosing for actual consumption, with high interest in getting something to eat after fasting

for four hours prior to the probe phase.

In conclusion, using stop-signals to influence choices by inducing automated avoidance of junk food in favor of healthier options is a promising tool in the fight against obesity. However, the timing of the stop-signal, the use of reinforcement and the number of stimuli must be optimized for cue-avoidance training to lead to a shift in choice. Further research is needed to elucidate the task parameters that lead to successful avoidance of items associated with stop-signals and the brain mechanisms responsible for avoidance behavior.

Chapter 5

Neural mechanisms of cue-approach training

5.1 Introduction

Previous research on value-based decision making has focused mostly on external reinforcement (Thorndike, 1911; O'Doherty et al., 2004) or the description of the decision problem (Tversky and Kahneman, 1986; Slovic, 1995; De Martino et al., 2006), but few have attempted to directly influence the underlying subjective values of individual options. In previous work by our group, we showed that these values can be influenced without relying on external reinforcement, simply by associating certain appetitive junk food items with a tone cue to perform a motor response (Schonberg et al., 2014a). The cue-approach task is the functional mirror of the cued inhibition version of the stop-signal task (Verbruggen and Logan, 2008; Lenartowicz et al., 2011). In the cue-approach task, participants are asked to fast for four hours prior to arriving for the experiment. After giving their consent, they are endowed with $3 to take part in an auction to obtain their pre-experimental preferences for 60 junk food items (Becker et al., 1964; Plassmann et al., 2007). Items are then rank ordered based on preference and median split into high and low value items. High and low value items are then placed into one of two experimental conditions: Go or NoGo. During training, participants passively view pictures

of food items and press a button when they hear an infrequent tone. In a subsequent probe phase, participants choose one item from a pair of equally preferred items, one associated with a tone during training (Go) and the other not associated with a tone (NoGo). Cue-approach training has proven to directly influence preference for single items through choice behavior following training. Approached items were chosen more often than initially equally preferred, non-approached items. This procedure successfully changed choice behavior and the effect was maintained over six to eight weeks for participants who underwent the longest training (Schonberg et al., 2014a). Such a shift in choice behavior is thought to be mediated by an increase in gain in the coding of value for Go items in the ventromedial prefrontal cortex (vmPFC), a brain region that has previously been heavily implicated in coding for value. This work has established cue-approach training as a model for non-reinforced preference change via modulation of subjective value for individual items.

Earlier imaging findings during the training phase of the cue-approach task were inconclusive. Follow-up behavioral studies using variations on the basic cue-approach training task have singled out memory and attention mechanisms to be at play during cue-approach training, leading to a shift in preferences at a later choice phase. In the current study, we sought to replicate previous behavioral and imaging findings, but the main goal was to investigate neural changes during the cue-approach training phase that might predict a later shift in choice preference using machine learning techniques.

Machine learning and pattern recognition algorithms have recently been

adapted and developed to decode and characterize cognitive task relevant neural activity using fMRI data (see Lemm et al., 2011; Mahmoudi et al., 2012, for review). One of the most popular of these machine learning techniques is linear classification. This is a simple technique for decoding information about task variables from patterns of activity across an array of voxels. One of the most common linear classification algorithms is the linear support vector machine (SVM). SVM can allow identification of task parameters from one set of neural activity patterns then to predict known task parameters based on a novel, never before seen pattern of neural activity. In this study, we sought to use linear support vector machine to train a classifier to identify whole brain fMRI patterns elicited by cognitive processes thought to be implicated during the cue-approach training task and leading to a shift in choice preference. Our hypothesis was that changes in classifier evidence for the cognitive processes of interest over time during the cue-approach training phase would predict later choices, reflecting a shift in preferences.

In this study, we developed a cognitive localizer task that engages three distinct cognitive processes thought to be implicated in value change during the cue-approach training task. We used multivariate pattern analysis techniques on fMRI data acquired during this novel cognitive localizer task to predict the level of engagement of these cognitive processes during cue-approach training. We investigated how changes in the level of engagement of these processes (as measured by classifier evidence) contributed to a shift in preferences at a later choice phase. We also used standard univariate techniques to replicate

previous imaging findings to further validate the cue-approach task.

5.2 Materials and Methods

5.2.1 Participants

32 healthy right-handed participants (17 female, mean age = 21.8 ± 3.1, age range: 18-29, mean body mass index (BMI) = 22.3 ± 3.8) completed a standard cue-approach task while in a magnetic resonance imaging (MRI) scanner.

All participants had normal or corrected-to-normal vision, no history of psychiatric, neurologic or metabolic illnesses, no history of eating disorders, no food restrictions, and were not taking any medications that would interfere with the experiment. Participants were also free of any metal implants or any other contraindications for MRI. Participants were told that the goal of the experiment was to study food preferences and were asked to refrain from eating for four hours prior to arrival at the laboratory (Plassmann et al., 2007). All participants gave informed consent and the internal review board (IRB) at the University of Texas at Austin approved the study.

5.2.2 Task

5.2.2.1 Auction

After consenting to take part in the study and filling out standard MRI safety metal screening forms, participants were endowed with $3, which they used to take part in an auction, as described in section 2.2.2.1. The auction

procedure allows us to obtain a measure of willingness to pay (WTP) for each of 56 appetitive junk food items per participant.

5.2.2.2 Item selection

Items were ranked based on WTP, where item #1 had the highest WTP and item #56 the lowest. 24 items with fixed rank order numbers from the full range were selected to serve as stimuli for the cognitive localizer task (see section 5.2.2.3). From the remaining 32 items, eight items were designated as higher-valued (from items ranked 8 through 18) and eight items as lower-valued (from items ranked 39 though 49). Out of each of these eight items, four were associated with an auditory cue (Go items) and four without any cue to press a button (NoGo items, Figure 5.1). This selection procedure ensured pairing of high-value Go with high-value NoGo items and low-value Go with low-value NoGo items such that items in each pair were roughly matched for WTP later presented at probe. Participants should a priori be indifferent in choosing between items in these pairs based on initially stated values. Of the 56 items used during auction, 24 were used during the cognitive localizer task and the other 32 items were used during training. Of those 32 items that were used during training, only 16 were used during probe phase (Figure 5.1B).To maintain 25% cue frequency as is standard in stop-signal tasks (Logan and Cowan, 1984), 16 out of 32 items not used during probe were NoGo items during training. Item assignment to Go and NoGo conditions to be used later in the probe phase was counterbalanced across participants.

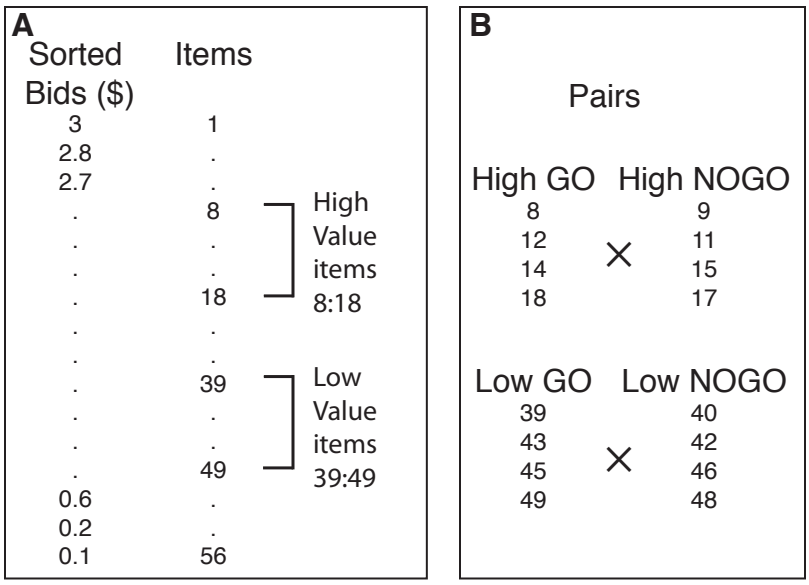

Figure 5.1: *Sorting and pair matching procedure used for cue-approach study in chapter 5. A) Items are rank ordered based on bid obtained in the auction (Figure 2.1A). Items are classified into high value (8:18) and low value items (39:49). B) 8 High and 8 low value items were assigned to one of two training conditions (Go, associated with a go-signal auditory cue and NoGo, not associated with a go-signal). Item Go/NoGo condition assignments were counterbalanced across participants.*

5.2.2.3 Cognitive localizer

In this task participants are presented with one food stimulus at a time and at the bottom of the screen one of three questions appears (Figure 5.2A). Participants are asked to answer the question relevant to the item on the screen. Each of 24 items appears with all three questions in random order over two runs. The three questions require three distinct cognitive processes to answer: 1) Valuation: "How much would you like to eat this item?" Four alternative forced choices are ranked from 1 (most) to 4 (least). 2) Memory

retrieval: "When did you last see this item at a store?" Four alternative forced choices from never to within the last week. 3) Perceptual decision: "How many items are outside the packaging?" Two alternative forced choices, either one or several items. Food stimuli appeared partially unwrapped with some of the product (either one or several pieces) appearing outside of the packaging. Stimuli appeared on the screen for a fixed duration of 3.6 seconds. Participants were asked to respond within that time limit and their responses were highlighted from the time they made a response until the end of the 3.6 second window, when the stimuli disappeared from the screen. Stimulus presentations were separated by a fixed inter stimulus interval (ISI) of 6 seconds consisting of a central fixation cross. Each of the two scan runs consisted of 36 trials lasting five minutes and fifty seconds.

5.2.2.4 Training

The cue-approach training task is the functional mirror of the stop-signal task (Logan and Cowan, 1984) and was developed by Schonberg et al. (2014a). For each trial, images of the food items were presented on the screen for 1.2 seconds followed by a fixed ISI of 3.6 seconds (Figure 5.2B). Item order was randomized within a block of 32 trials. Participants were instructed to press a button on the keypad as fast as possible only when they heard an infrequent neutral tone and before the item disappeared from the screen. Items that were assigned to the Go condition were consistently associated with the tone. The tone appeared on average 950 ms after the item was presented on

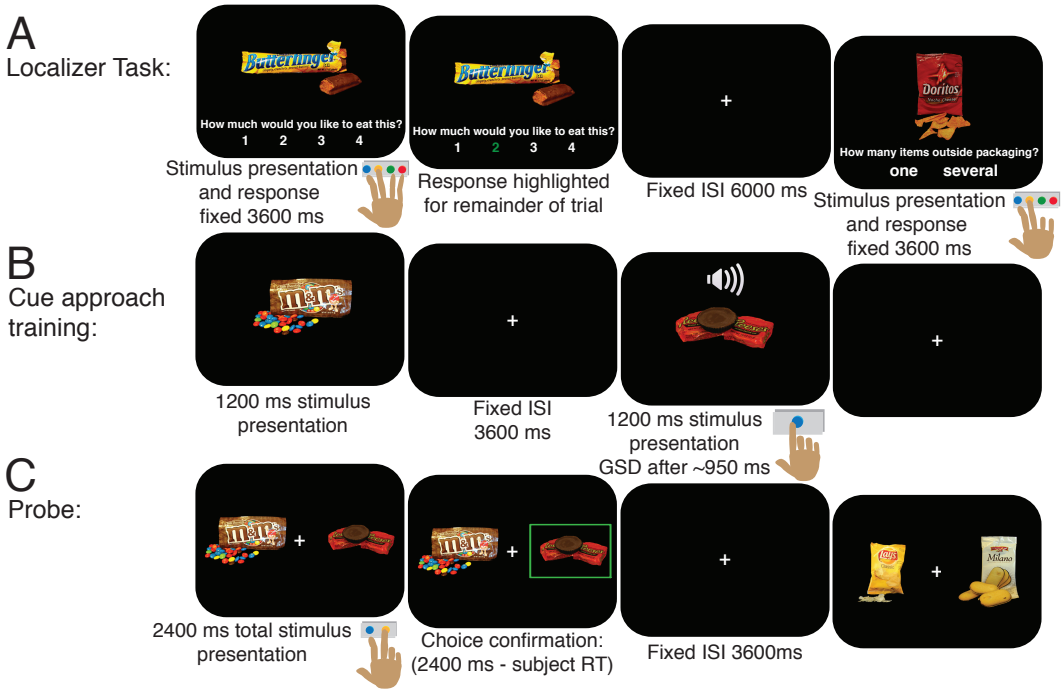

Figure 5.2: *Cue-approach task procedure for study in chapter 5. A) Cognitive localizer task. Food items appeared on the screen one at a time, at the bottom of the screen one of three questions appeared. Participants were asked to answer the question relevant to the item on the screen within 3600 ms, at which time the trial ended. Successive stimulus presentations were separated by a fixed ISI of 6 s. B) Cue-approach training. Single food items appeared on the screen for a fixed 1200 ms. Participants were asked to press a button on the keypad as quickly as possible only when they heard a neutral tone that sounded on average 950 ms after food stimulus onset (GSD). Stimulus presentations were separated by a fixed 3600 ms ISI. D) Probe task. Participants chose between two items on the screen. They were told that their choice on a random probe trial would be honored at the end of the experiment. Choices had to be made within 2 s of trial onset.*

the screen (Go-signal delay, GSD). GSD was adjusted using a ladder technique. We increased the GSD by 17 ms if participants pressed the button before the item disappeared (to make the task more difficult) and reduced GSD by 50

ms if the participant failed to press the button or pressed it after the item disappeared (to make the task easier). We chose this 3:1 ladder titration ratio to ensure a 75% success rate in button presses. All 32 food items used during training were presented 12 times each during training. Each of the six scan runs consisted of two presentations of each stimulus (i.e. 64 trials) lasting five minutes and twelve seconds.

5.2.2.5 Probe

At the end of training, participants filled out a computer-adapted version of the Barratt impulsiveness scale (BIS-11) questionnaire (Patton et al., 1995) while undergoing a structural scan. They were then presented with pairs of food items in a probe task (Figure 5.2C). Items in each pair were matched for WTP and made up of one Go and one NoGo item (Figure 5.1B). Participants were told that a single trial would be drawn at random at the end of the session and their choice on that trial would be honored (i.e. they would receive the item that they chose on the randomly selected trial at the end of the experiment and remain in the lab to consume it). Pairs of items were presented on the screen for 2400 ms. Item selection was confirmed with a green rectangle drawn around the selected item, which remained in evidence from response time to the end of the 2400 ms trial window. If participants failed to make a choice within two seconds, a brief message asking them to please respond faster appeared for 400 ms. Consecutive stimulus presentations were separated by a fixed ISI of 3600 ms. Each unique pair of items was presented

in random order twice during probe (i.e. 64 trials) for a scan run duration of six minutes and 24 seconds.

5.2.3 fMRI Acquisition

Imaging data were acquired on a 3 T Siemens Skyra MRI scanner with a 32-channel head coil. Functional data were acquired using a T2*-weighted echo planar imaging sequence (repetition time (TR) = 1200 ms, echo time (TE) = 30 ms, flip angle (FA) = 63, field of view (FOV) = 230 mm, acquisition matrix of 96 x 96. 64 oblique axial slices with a 2.4 mm in-plane resolution positioned 30° off the anterior commissure-posterior commissure line to reduce the frontal signal dropout (Deichmann et al., 2003) and spaced 2 mm with a 0.4 mm gap to achieve full brain coverage). Slices were acquired using the multi-band sequence (Moeller et al., 2010, acceleration factor = 2, parallel imaging factor iPAT = 2) in an interleaved fashion. Higher-order shimming was used to reduce susceptibility artifacts. Each of the localizer runs consisted of 292 volumes, each of the training runs consisted of 260 volumes, and the probe run consisted of 324 volumes. In addition to functional data, a single three-dimensional high-resolution full brain image was acquired using a magnetization prepared rapid gradient echo (MPRAGE) pulse sequence (TR = 2400 ms, TI = 1000 ms, TE = 1.94 ms, FA = 8, FOV = 205 mm, voxel size = 0.8 x 0.8 x 0.8 mm) for brain masking and image registration.

5.2.4 Analysis

5.2.4.1 Behavioral Analysis

Probe To test whether cue-approach training induced a preference change, we performed repeated-measures logistic regression to compare the odds of choosing the Go to NoGo items against equal odds for the high-value and low-value pairs separately. We also performed repeated-measures linear regression to test for differences in reaction time (RT) for choices of Go and NoGo items for the high-value and low-value pairs separately.

Auction We ran repeated-measures linear regression to test the two-way interaction between time (pre-training/post-training auction) and condition (Go/NoGo) on WTP within high-value and low-value items separately. This interaction tests whether the change in WTP over time is different for Go and NoGo items. P values for the effects in the mixed models were calculated using the Kenward-Roger approximation for degrees of freedom (Kenward and Roger, 1997).

5.2.4.2 Eyetracking Analysis

Eye-tracking data were acquired using an MRI compatible SR-Research Eyelink-1000 eye tracker. Usable data were obtained on 14 participants. Gaze position was categorized as being either within the x-axis boundaries of the fixation cross, within the x-axis boundaries of the stimulus on the right of the fixation cross or on the left of the fixation cross. The proportion of the decision time spent looking at the right or left items on each trial was calculated. We examined the difference in the proportion of total decision time spent looking

at the Go item versus the NoGo item, when the participant chose the Go or the NoGo item separately using repeated measures linear regression. We also examined the difference in the proportion of time spent looking at the Go versus the NoGo item when that item was not chosen using repeated-measures linear regression. Finally, we looked at the main effect of Go/NoGo item assignment as well as the main effect of chosen/unchosen on the proportion of choice time spent viewing an item during probe phase using repeated measures linear regression including the two factors Go/NoGo and chosen/unchosen with a grouping factor for participants.

5.2.4.3 Imaging Analysis

Imaging Data Preprocessing Raw imaging data in DICOM format were converted to NIFTI format and preprocessed through a standard preprocessing pipeline using the FSL package version 5 (Smith et al., 2004). Functional image time series were first aligned using the MCFLIRT tool to obtain six motion parameters that correspond to the x-y-z translation and rotation of the brain over time. Second, the skull was removed from the T2* images using the brain extraction tool (BET) and from the high-resolution T1 images using Freesurfer (Ségonne et al., 2004; Dale et al., 1999). Spatial smoothing was performed using a Gaussian kernel with a full-width half maximum (FWHM) of 5 mm. Data and design matrix were high-pass filtered using a Gaussian-weighted least-squares straight line fit with a cutoff period of 100 s. Grand-mean intensity normalization of each run's entire four-dimensional

data set by a single multiplicative factor was also performed. The functional volumes for each participant and run were registered to the high resolution T1-weighted structural volume using a boundary-based registration method implemented in FSL5 (BBR Greve and Fischl, 2009). The T1-weighted image was then registered to the MNI152 2 mm template using a linear registration implemented in FLIRT (12 degrees of freedom). These two registration steps were concatenated to obtain a functional-to-standard space registration matrix.

Masks and regions of interest Previous studies have implicated the ventromedial prefrontal cortex (vmPFC) in coding for value (Plassmann et al., 2007; Tom et al., 2007; Chib et al., 2009; McNamee et al., 2013). Thus, we focused our imaging analyses during the probe and training phases below on that region (small volume correction) and employed an extensive anatomical mask of medial prefrontal cortex (mPFC) generated from the Harvard-Oxford atlas and previously used by our group in Schonberg et al. (2014a). We also used two additional independent regions of interest (ROI1 and ROI2) in the vmPFC to extract percentage signal change (PSC) over the analyzed events during training and probe phases. Mean PSC was calculated in relation to mean intensity across time so that zero represents the resting baseline. ROI1 was generated from a cluster in the vmPFC (thresholded at $z = 2.3$) for the parametric effect of the modulation of BOLD by responses to the valuation question during the cognitive localizer task (Figure 5.4A). ROI2 was gener-

ated from a large cluster in vmPFC (thresholded at z = 4.3) for the memory retrieval task related activity greater than valuation and perceptual decision activity combined (Figure 5.4B).

Cognitive Localizer We conducted a GLM analysis on the cognitive localizer task data. The GLM model included eight regressors of interest: (i) onsets for valuation trials, modeled with a duration which equaled the average RT across all trials and participants; (ii) same onsets and duration as i but modulated by response (1 for like least to 4 for like most) demeaned across these trials; (iii) onsets for perceptual decision trials modeled with the same duration as above; (iv) same onsets and duration as iii but modulated by response (1 for single item and 2 for several items outside of packaging) demeaned across these trials; (v) onsets for memory retrieval trials modeled with the same duration as above; (vi) same onsets and duration as v but modulated by response (1 never saw this item in a store to 4 seen it within the last week) demeaned across these trials; (vii) to account for any differences in RT between trial types we added a regressor with the onsets of all valid trials and the same duration as all other regressors, while the modulator was the demeaned RT across all valid trials; (viii) onsets for missed trials. We included the six x, y, z translation and rotation motion parameters obtained from MCFLIRT, framewise displacement (FD) and RMS intensity difference from one volume to the next (DVARS Power et al., 2012) as confound regressors. We also modeled out trials with FD and DVARS that exceeded a threshold of 0.5 by adding

a single time point regressor for each "to-be-scrubbed" volume (Siegel et al., 2013). All regressors were entered at the first level of analysis and all (but the added confound regressors) were convolved with a canonical double-gamma hemodynamic response function. The temporal derivative of each regressor (but the added confound regressors) was included in the model. The model was estimated separately for each participant and each run.

Probe In line with the work we had previously carried out exploring the neural signature of value change following cue-approach training (Schonberg et al., 2014a), we focused our univariate analysis in the current study on the probe phase. We used a general linear model (GLM) for the probe phase that included seven regressors for each of the two trial types. For high-value Go versus high-value NoGo, (i) onsets of trials when high-value Go items were chosen with fixed duration, which was the average RT across all trials and participants; (ii) to explore the preference for each item, we used the demeaned total number of choices (on all probe trials where this item appeared) for the chosen item as a parametric modulator of the above onset regressor, with the same average RT as above used for duration; (iii) to account for the difference in pre-training WTP between the items in each pair we added the WTP difference as a parametric modulator with the same onsets and durations as regressor (i). All of the above three regressors were added for trials when participants chose the NoGo item in a pair. To account for RT differences between choices of the Go and NoGo items we added a regressor with the onsets of all

high-value Go and NoGo trials but as the modulator we added the demeaned RT across all these trials. We defined the same seven regressors for the probe trials that compared low-value Go to low-value NoGo, which resulted in a total of 15 regressors (two trial types times seven) and an additional regressor for missed trials of all types. The same motion, FD and DVARS confound regressors described above were included.

To test which regions showed greater modulation by preference for an item, we contrasted the parametric modulator of the chosen high-value Go items (regressor (ii) above) with the same regressor for the high-value NoGo items. We masked this contrast by our pre-hypothesized anatomical mPFC region. The mask was the same as that previously used in Schonberg et al. (2014a) and encompassed the medial PFC by combining Harvard-Oxford regions (frontal pole, frontal medial cortex, paracingulate gyrus and subcallosal cortex) falling between x = 14, y = -14 and $z < 0$.

Ten participants were excluded from the imaging analysis because their parametric modulator of choices had zeroed out. Two chose all high-value Go items in exactly the same proportions and three chose all high-value NoGo items in the same proportions during probe. One participant chose all low-value Go and four others chose all low-value NoGo items in exactly the same proportions. Thus, the parametric modulator was perfectly correlated with the intercept regressor (column of ones) resulting in a rank-deficient design matrix.

For all group analyses we averaged across individual subjects by per-

forming a one-sample t-test to obtain the overall effects for the group. All reported statistical maps were corrected at the whole-brain level using a cluster-based Gaussian random field correction for multiple comparisons, with an uncorrected cluster-forming threshold of $z = 2.3$ and corrected extent threshold of $p < 0.05$, except for the comparison between preference modulation of Go and NoGo during probe, which was small volume corrected only for the anatomical medial PFC mask. Additionally, we extracted PSC from the independent ROI1 and ROI2 described above.

Training The GLM during the training phase included 4 regressors for each Go item broken down by the two subsequent probe trial types (high-value Go versus high-value NoGo and low-value Go versus low-value NoGo): (i) onsets of the Go trial, modeled with a fixed duration of 1.2 seconds; (ii) same onset and duration but modulated by subsequent number of times chosen during probe; (iii) same onset and duration but modulated by initial WTP; (iv) same onset and duration but modulated by the Go-signal delay for that trial. Thus there were two different Go trials and for each there were four regressors yielding a total of 8 regressors. Then for each of the different types of NoGo trials there were three regressors similar to above except for modulation by Go signal delay as there was no go-signal in the NoGo trials. Thus, there were two different NoGo trials and for each there were three regressors yielding a total of 6 regressors. Additionally, for each high-value and low-value item that was not used during probe, we included the equivalent to regressors i and iii above

to yield four additional regressors. To account for RT differences between all trials we added a regressor with the onsets of all Go trials and the modulator was the demeaned RT across all these trials. We further added a missed trial regressor each for high-value Go and low-value Go as well as two regressors for an erroneous response for high-value and low-value NoGo trials. There were a total of 23 regressors. We added the same covariates as in the probe design matrix, including the six motion regressors described above, along with FD and DVARS as confound regressors.

Multivoxel pattern analysis In addition to the GLM analysis, we performed a multivoxel pattern analysis (MVPA) to classify the pattern of activation during each of the three cognitive processes engaged during the three trial types in the cognitive localizer task. We used whole brain raw parameter estimates obtained from the cognitive localizer task GLM described above as input into a three-class SVM classifier to classify the pattern for each of valuation, perceptual decision and memory retrieval cognitive processes. We then conducted two-way cross validation, where we trained the classifier on the first half of the cognitive localizer neural data and tested it on the second half, then vice versa to obtain average classifier cross validation accuracy. Once we ascertained that the cross-validation accuracy surpassed chance classification, we then trained the classifier on all the neural data and applied the classifier on raw parameter estimates extracted from the GLM on cue-approach training task data to obtain classifier evidence for each of valuation, perceptual

decision and memory retrieval at each cue-approach training trial per participant. We ran this analysis in order to look at changes in classifier evidence corresponding to each of the cognitive processes thought to be engaged during cue-approach and determining whether this change predicts choice at probe.

5.3 Results

5.3.1 Behavioral Results

Consistent with previous findings, we found an effect of cue-approach training on choices during the probe phase (Figure 5.3A). Participants chose high-value Go over high-value NoGo items on 65% of trials (odds ratio (O.R) = 2.21, 95% Confidence Interval (C.I) = [1.48 3.29], $p < 0.0001$). Also consistent with some previous findings when cue-approach training included a reduced stimulus set as is the case in this study, participants chose low-value Go over low-value NoGo items on 60% of trials (O.R = 1.7, C.I = [1.13 2.56], $p = 0.01$). However the Go choice effect was larger for high-value than for low-value pairs ($p = 0.001$).

We repeated the initial auction after probe to test whether the subjective value placed on individual items changed after training. Although we had previously reported evidence that cue-approach training influenced the value of individual items, we failed to replicate that finding in this study. WTP for high-value Go and NoGo items regressed equally toward the mean and WTP for low-value Go and NoGo items also increased equally and regressed toward the mean. There was a main effect of time (pre- to post- training, $p < 0.0001$),

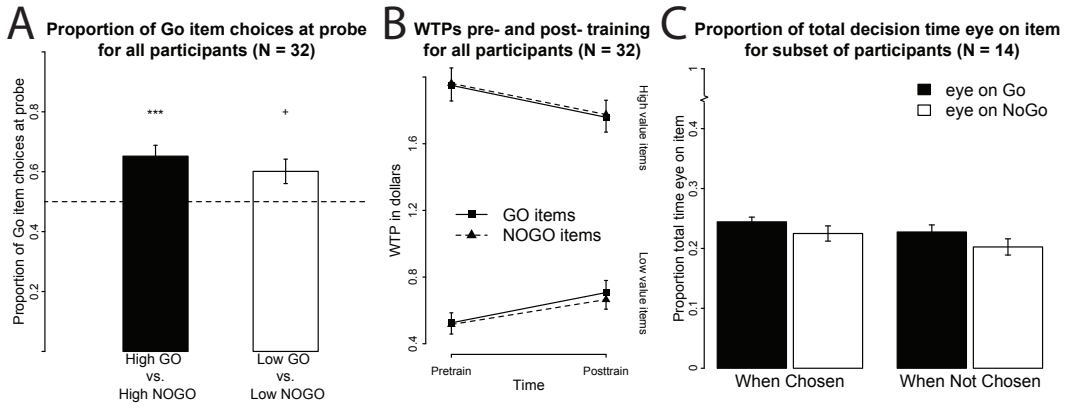

Figure 5.3: *Behavioral results for cue-approach and cue-avoidance studies. A) Proportion of choices of the Go item in pairs of high-value Go versus NoGo and low-value Go versus NoGo items for all participants. Significance level reflects odds of choosing the Go to NoGo item. B) WTP before and after cue-approach training for Go and NoGo separately for items in the probe high-value Go versus high-value NoGo pairs (top) and low-value Go versus low-value NoGo pairs (bottom). The sample includes all participants. C) Proportion of total choice time during probe that gaze position was on the Go or NoGo item in a pair separately for trials when the items were chosen and not chosen. The sample is a subset of all participants (N = 14). Error bars represent one standard error of the mean (SEM) in A and within-subject SEM in B and C. ***: $p < 0.0001$, $^{+}$: $p < 0.05$ (two-sided tests).*

but no main effect of training condition (Go or NoGo) or interaction between the factors on WTP (p's > 0.5).

Previous work shows that participants spend more time fixating on an item before choosing it compared to unchosen alternatives (Krajbich and Rangel, 2011; Schonberg et al., 2014a). In the current study, we confirm this result on a subset of the participants on whom we collected eye tracking data (Figure 5.3C). Consistent with methods previously described in Schonberg et al. (2014a), we calculated the proportion of time participants spent view-

ing a particular item as the total duration that the gaze position was within the bounds of a food item on the screen, divided by the reaction time. In a repeated-measures linear regression comparing proportion of time spent viewing an item against Go/NoGo and chosen/unchosen factors (with a grouping factor for participant), we found a main effect of chosen/unchosen ($p = 0.01$) and Go/NoGo ($p = 0.02$). As we have observed in previous studies, participants tended to spend a larger proportion of the total gaze time on the chosen versus unchosen item during the choice window regardless of whether the chosen item was a Go or NoGo item. We previously reported a significant difference in gaze time between unchosen Go and unchosen NoGo items, suggesting that cue-approach training drove attention toward the Go items in the subsequent choice phase even when participants did not choose these items. With lower power due to a small sample size, we failed to fully replicate that result in the current study. It is however worth noting that the result is slightly trending toward significance at $p = 0.09$ when restricting the analysis to high-value items.

5.3.2 Imaging Results

5.3.2.1 Univariate Results

Cognitive Localizer Task BOLD activity was related to responses to the question "How much would you like to eat this item?" during the cognitive localizer task, with responses indicating higher preference being related to higher activity in the ventromedial prefrontal cortex (vmPFC), but also in

the left dorsolateral prefrontal cortex, right inferior frontal and cingulate cortices, as well as lateral parietal and medial occipital cortices (Figure 5.4A and Table 5.1). ROI1 was generated using this contrast from the vmPFC cluster (cluster number 2 in Table 5.1), serving to extract percentage signal change (PSC) for analyses below.

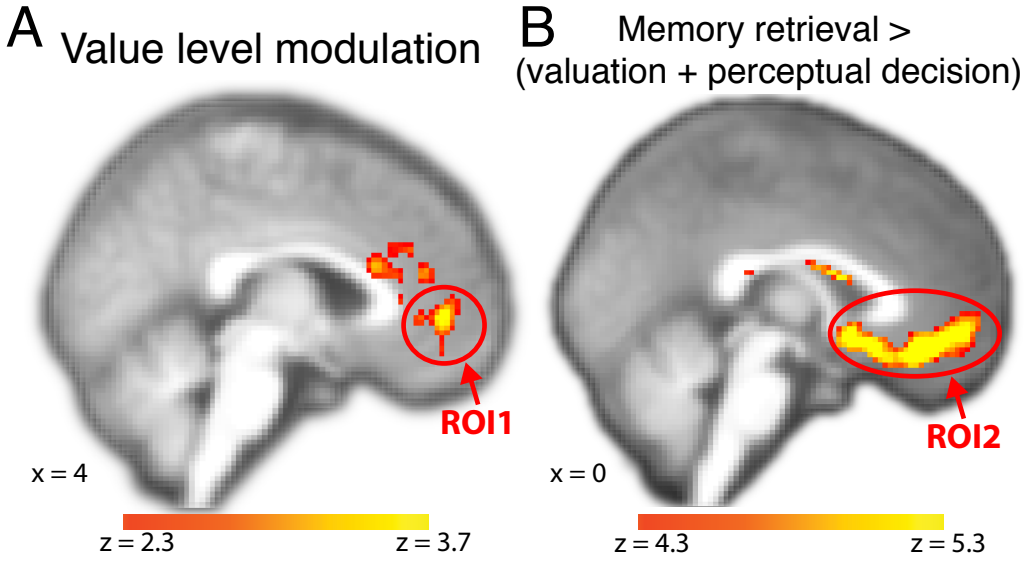

Figure 5.4: *Imaging results from the cognitive localizer task. A) Parametric effect of the relationship of coded responses to the valuation question (1 least to 4 most) and BOLD. Circled cluster in vmPFC was binarized to create ROI1. B) Memory retrieval related activity greater than valuation and perceptual decision. Circled cluster in vmPFC was binarized to create ROI2. Coordinates reported in standard Montreal Neurological Institute (MNI) space. Heatmap color bars range from z-stat = 2.3 to 3.7 in A and z-stat = 4.3 to 5.3 in B. These maps were cluster-corrected at a whole-brain level $p < 0.05$, two sided linear regression.*

BOLD activity was higher when participants answered the question

Cluster number	Region	# voxels in region	Cluster size	x	y	z	Peak Z
1	L Lingual Gyrus	872	1989	-10	-74	-2	6.92
	L Intracalcarine Cortex	431					
	L Occipital Fusiform Gyrus	178					
	L Occipital Pole	102					
	R Lingual Gyrus	45					
	L Precuneous Cortex	12					
	L Supracalcarine Cortex	10					
2	L Paracingulate Gyrus	175	538	0	50	2	4.35
	R Paracingulate Gyrus	116					
	L Frontal Pole	79					
	L Anterior Cingulate Gyrus	74					
	R Anterior Cingulate Gyrus	42					
3	R Anterior Cingulate Gyrus	171	435	-2	36	20	3.98
	L Anterior Cingulate Gyrus	113					
	L Paracingulate Gyrus	80					
	R Paracingulate Gyrus	38					
4	R Angular Gyrus	156	430	64	-50	18	3.39
	R Middle Temporal Gyrus	155					
	R Posterior Supramarginal Gyrus	73					
	R Superior Lateral Occipital Cortex	16					
	R Inferior Lateral Occipital Cortex	12					
5	L Posterior Supramarginal Gyrus	241	382	-54	-44	48	4.05
	L Angular Gyrus	65					
	L Anterior Supramarginal Gyrus	49					
	L Superior Lateral Occipital Cortex	18					
6	R Pars Triangularis	161	380	50	28	0	3.93
	R Pars Opercularis	50					
	R Insular Cortex	44					
	R Frontal Operculum Cortex	31					
	R Frontal Pole	25					
	R Central Opercular Cortex	21					
	R Frontal Orbital Cortex	10					
7	L Middle Frontal Gyrus	244	378	-34	30	46	4.11
	L Superior Frontal Gyrus	80					

Table 5.1: *Results from analysis of preference-related modulation of activity during the cognitive localizer task (Figure 5.4A, $p < .05$, corrected); regions presented here demonstrated positive relationship with responses to valuation question. For each cluster, the list shows all regions from the Harvard-Oxford atlas that contained more than 10 voxels within that cluster, along with the peak X/Y/Z location for the cluster in MNI space.*

"When did you last see this item at a store?" and retrieved that memory than when they answered either of the other two questions during the cognitive localizer task which engaged valuation and perceptual decision circuitry in several areas in the brain (Figure 5.4B and Table 5.2). These regions included

primarily a large swath of the medial prefrontal cortex and cingulate cortex, but also hippocampus, medial and lateral parietal cortices as well as lateral temporal cortex. ROI2 was generated using this contrast from the vmPFC cluster (subset of cluster number 1 in Table 5.2) and used to extract PSC for the analyses below.

Probe We used the number of times a particular item was chosen at probe as a parametric modulator to look at whether the vmPFC represents post-training value during probe in our task. The vmPFC has previously been heavily implicated in coding for value. In line with methods we've previously used, we limited our analysis to a large anatomical area within mPFC. There were no whole brain corrected or small volume corrected (SVC) results for modulation of vmPFC BOLD by post-training preference for high-value Go items. Additionally, unlike previous findings in Schonberg et al. (2014a), the relationship between preference and BOLD in the vmPFC did not differ for choices of high-value Go and high-value NoGo items. We conducted an ROI analysis and extracted the mean PSC from Go and NoGo choice events. The ROIs used were determined from the cognitive localizer task described above. Mean PSC for high-value Go and NoGo choice trials did not differ (left two bars in Figures 5.5A and B).

There was no significant effect within the vmPFC for the modulation of BOLD by preference for low-value Go or NoGo items. However, the relationship between BOLD and preference was more positive for low-value Go than

Cluster number	Region	# voxels in region	Cluster size	x	y	z	Peak Z
1	R Frontal Pole	2235	18763	4	42	-12	7.42
	L Frontal Pole	2177					
	L Superior Lateral Occipital Cortex	932					
	L Superior Frontal Gyrus	816					
	R Paracingulate Gyrus	663					
	L Paracingulate Gyrus	644					
	R Superior Frontal Gyrus	625					
	L Angular Gyrus	517					
	L Precuneous Cortex	499					
	L Middle Frontal Gyrus	496					
	R Subcallosal Cortex	416					
	L Posterior Cingulate Gyrus	370					
	L Subcallosal Cortex	321					
	R Frontal Medial Cortex	302					
	L Frontal Medial Cortex	254					
	R Posterior Cingulate Gyrus	232					
	R Precuneous Cortex	155					
	R Anterior Cingulate Gyrus	125					
	R Middle Frontal Gyrus	113					
	L Anterior Cingulate Gyrus	86					
	L Posterior Supramarginal Gyrus	84					
	Left Hippocampus	31					
	L Posterior Parahippocampal Gyrus	17					
	Left Accumbens	15					
	L Planum Temporale	12					
	Left Caudate	11					
	L Parietal Operculum Cortex	10					
	Right Caudate	10					
2	R Posterior Middle Temporal Gyrus	600	2884	66	-4	-14	5.66
	R Posterior Superior Temporal Gyrus	433					
	R Central Opercular Cortex	310					
	R Anterior Middle Temporal Gyrus	196					
	R Parietal Operculum Cortex	184					
	R Planum Temporale	164					
	R Anterior Superior Temporal Gyrus	136					
	R Temporal Pole	120					
	R Insular Cortex	109					
	R Heschl's Gyrus	67					
	R Postcentral Gyrus	51					
	R Precentral Gyrus	41					
	R Planum Polare	36					
	R Posterior Inferior Temporal Gyrus	30					
3	L Posterior Middle Temporal Gyrus	726	2101	-62	-12	-14	5.48
	L Posterior Middle Temporal Gyrus	726					
	L Anterior Middle Temporal Gyrus	357					
	L Temporal Pole	244					
	L Anterior Superior Temporal Gyrus	118					
	L Central Opercular Cortex	87					
	L Posterior Superior Temporal Gyrus	80					
	L Precentral Gyrus	54					
	L Posterior Inferior Temporal Gyrus	40					
	L Postcentral Gyrus	17					
4	R Postcentral Gyrus	758	1252	22	-44	70	4.91
	R Precentral Gyrus	180					
	R Superior Parietal Lobule	172					
5	R Superior Lateral Occipital Cortex	491	969	52	-58	28	5.56
	R Angular Gyrus	451					
6	Cerebellum	935	935	46	-72	-38	5.12
7	Right Hippocampus	243	450	20	-18	-16	5.18
	Right Amygdala	40					
	R Anterior Parahippocampal Gyrus	25					
8	Left Hippocampus	208	339	-18	-20	-18	5.14
	L Posterior Parahippocampal Gyrus	35					
	L Anterior Parahippocampal Gyrus	27					

Table 5.2: *Results from analysis of memory retrieval-related activity during the cognitive localizer task (Figure 5.4B, $p < .05$, corrected); regions presented here demonstrated higher activity for memory retrieval than valuation and perceptual decision combined. For each cluster, the list shows all regions from the Harvard-Oxford atlas that contained more than 10 voxels within that cluster, along with the peak X/Y/Z location for the cluster in MNI space.*

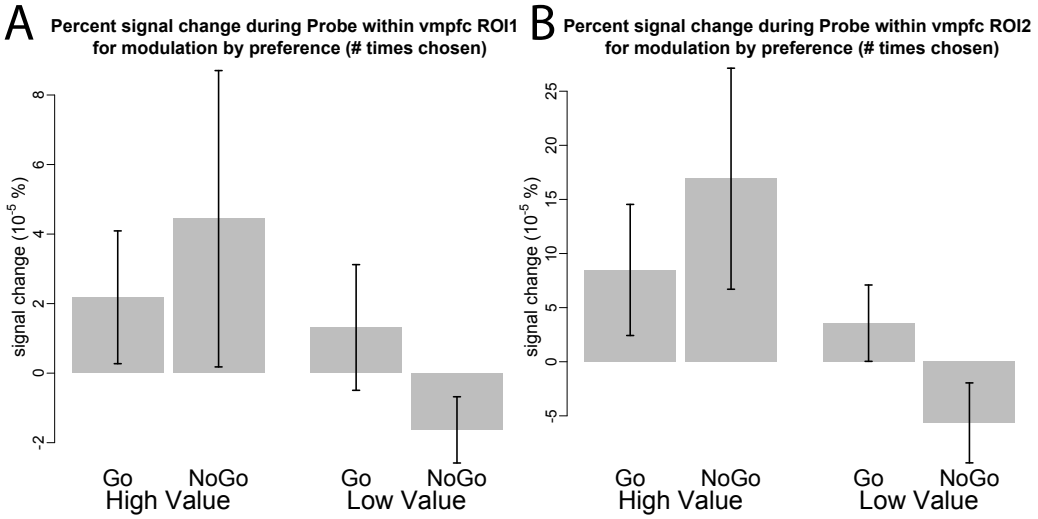

Figure 5.5: *Activity within vmPFC ROI1 (A) and ROI2 (B) determined from the cognitive localizer task during probe for modulation by number of times an item was chosen. Bars represent percentage signal change (PSC) for the relationship between BOLD and preference (i.e. number of times item was chosen at probe) separately for probe trials when high- or low-value Go or NoGo items were chosen. Error bars represent one SEM*

for low-value NoGo when restricting the analysis to an extensive anatomical mask of mPFC (SVC). This difference was also reflected in PSC extracted from the vmPFC ROIs determined from the cognitive localizer task (right two bars in Figures 5.5A and B). This difference was not present in our previous study.

Training There were no differences in the Go stimulus onset driven activations for the last run of training compared to the first run, consistent with previous findings. This is likely due to the fact that no choices were required during the training phase. We also used the same parametric modulator as in

the probe phase (i.e. the number of times a particular item was chosen) to look at any preference related signals during the last run of training. There was no effect within the vmPFC for the modulation of BOLD response by preference for any of high- or low-value Go or NoGo items. The lack of effect here fails to replicate previous findings. Additionally, the relationship between BOLD and preference for high-value and low-value Go vs. NoGo were no different, replicating previous findings. The lack of differences between Go and NoGo in the relationship between BOLD and preference was confirmed by extracting signals from the independent vmPFC ROIs determined from the cognitive localizer task above (Figure 5.6).

5.3.2.2 MVPA Results

When we trained the classifier on half the cognitive localizer task fMRI data to identify activation patterns for valuation vs. perceptual decision vs. memory retrieval cognitive processes, and applied the classifier on the other half of the data, we obtained better than chance classification accuracy (65.8% average cross-validation accuracy while chance is 33%). Thus, we were able to reliably classify the activation patterns elicited by three cognitive processes thought to be involved during the cue-approach training task and to contribute to a change in preferences. However, when we trained the classifier on all the cognitive localizer task fMRI data and then applied the classifier to fMRI data acquired during the cue-approach training task to predict the extent to which

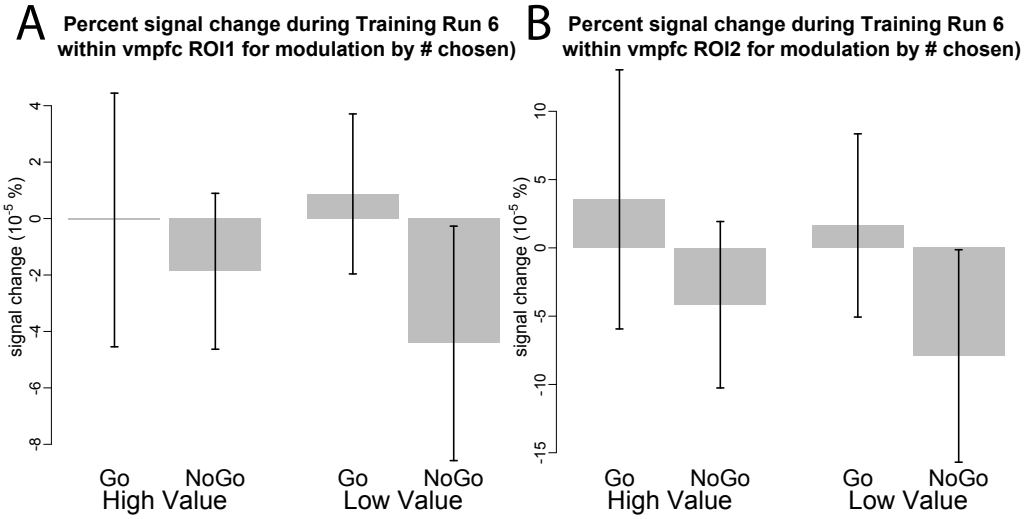

Figure 5.6: *Activity within vmPFC ROI1 (A) and ROI2 (B) determined from the cognitive localizer task during the last run of training for modulation by number of times an item was chosen. Bars represent PSC for the relationship between BOLD and preference (i.e. number of times an item was chosen at probe) separately for high- and low-value Go or NoGo training trials on the last run of training. Error bars represent one SEM*

each of the cognitive processes of interest were elicited across training trials, we did not see any notable differences between the estimates across training trials or between trial types (Figure 5.7).

In a linear regression mixed model, there was no main effect of valuation classifier evidence from the last presentation during the training phase on subsequent choice during probe, but there was a weak interaction ($p = 0.03$) between valuation classifier evidence from the last presentation during training phase and item type (high-value Go/NoGo) on subsequent choice during probe. This means that the item by item relationship between valuation classifier

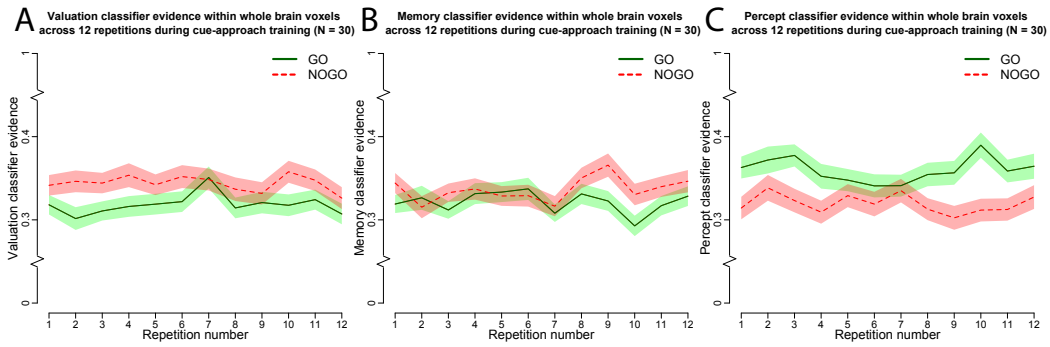

Figure 5.7: *MVPA classifier evidence during cue-approach training. Three-class SVM classifier was trained on cognitive localizer neural data and applied to each trial of cue-approach training to obtain classifier evidence for each class split by training trial type (Go green solid line or NoGo red dashed line): A) valuation, B) memory retrieval and C) perceptual decision. Shaded area represents one within-participant SEM per presentation block during training.*

evidence on the last presentation during the training phase and subsequent choices during probe was different for high-value Go and NoGo items. This interaction effect did not hold for the first presentation (although there was no three way interaction between valuation classifier evidence x item type [high-value Go/NoGo] x presentation number [first/last]). The interaction also did not hold for low-value Go vs. NoGo, and did not hold when using memory retrieval or perceptual decision classifier evidence.

5.4 Discussion

Previous work by our group has established the cue-approach training task as a viable paradigm to influence choice behavior without reverting to effortful self-control and external reinforcement. The exact neural mechanism

responsible for a shift in preferences following cue-approach training remains unknown. In the current study, we sought to investigate neural changes during cue-approach training that predict subsequent choices. Although we were not able to fully answer the questions we initially set out to elucidate, likely due to technical reasons, we partially replicated previous findings. The implications of current findings (and lack of results) combined with other findings not elaborated in this chapter are discussed.

We designed a cognitive localizer task that engages three distinct cognitive processes thought to be implicated during cue-approach training to influence subsequent choices. We built a classifier to distinguish between whole brain patterns of activity elicited by the three cognitive processes of interest. This classifier would in theory then have allowed us to obtain a measure of the degree to which each of these cognitive processes were engaged during cue-approach training. Any changes in the obtained classifier evidence measure could then be regressed against choices at probe. Classification was well above chance in a standard two-way cross-validation. However, the classifier did not appear to generalize from the localizer task to the cue-approach task. Classifier evidence for the three classes during the cue-approach training task were all at chance throughout all training runs. The localizer and cue-approach tasks are very different. The localizer task asks participants to process images of food items and answer two or four alternative forced choice questions, whereas during the cue-approach training task, participants are asked to simply view images of food unless they hear a tone which cues them to press a button. It

appears that the patterns of activity elicited by potentially shared cognitive processes do not overlap enough to solve the classification problem posed.

We have however partially replicated previous behavioral and imaging findings. The current study replicates the now well established cue-approach effect. In the probe phase, participants chose items that were previously associated with a cued button press during the training phase over items that were not associated with a cue but that were matched for pre-experimental preference. Several other studies not covered in this chapter were conducted in order to narrow down the possible mechanisms engaged during cue-approach training to cause a preference shift. These studies have concluded that a cued motor response that requires sustained attention prior to the cue is necessary to induce a change in choice behavior. Indeed, a cue alone without a motor response or an uncued motor response alone during the training phase are not sufficient to bias choices. Furthermore, eliminating the go-signal delay and sounding the cue to make a motor response concurrently with the onset of food stimuli without delay during the training phase eliminated the choice effect at probe. Finally, requiring participants to make choices using eye movements rather than manual button presses revealed a preference shift following standard cue-approach training involving a cued manual motor response with the cue appearing after the food stimulus is shown. This last result provides evidence that the choice shift was not calculated within manual or ocular motor circuits but rather that the shift in preference is likely due to modulation of more general value coding regions in the brain such as vmPFC. Taking

these results together, we are confident that cue-approach training engages attentional mechanisms during behaviorally relevant points in time in order to modulate value coding of items that were associated with the Go signal.

Previous findings point to a more positive relationship between BOLD activation in the vmPFC and preference for choices of high-value Go when compared to choices of high-value NoGo items. This finding was not replicated in the current study. Failure of replication could be due to low power, reduced variance in the choice measure or poorer signal-to-noise ratio (SNR) in the vmPFC. Our complete sample included 32 participants, which is considered adequate for fMRI studies. However, our contrasts of interest were based on participant behavior and we had to exclude participants who chose items within a category at the same rate, which represented a larger proportion of the sample than in a previous imaging study, significantly reducing our power to detect an effect. During the cognitive localizer task, there was a strong relationship between responses rating how much participants wanted to eat an item and signal in the vmPFC, attesting to adequate SNR in that region. However, participants more directly generate specific value for an item during the localizer task, whereas they are comparing the relative value of two items during the probe task.

The cue-approach task continues to prove to be a useful paradigm for behavioral change. Its non-reliance on effortful self control and its targeting of automatic processes in the brain render it particularly appealing. This research shows promise for the development of new real-world, non-externally

reinforced behavioral change paradigms by tapping attentional and memory mechanisms that act at behaviorally relevant points in time to modify valuation of particular stimuli.

Chapter 6

Spacing of cue-approach training

6.1 Introduction

The potential for targeting automatic processes to change human behavior has become increasingly clear (Marteau et al., 2012), especially in light of the relative ineffectiveness of relying on effortful control of behavior, given the largely automatic and habitual nature of everyday human behavior (Neal et al., 2006). Previous research aimed at changing choice preference for appetitive junk food employed a novel non-reinforced training paradigm called cue-approach training (Schonberg et al., 2014a). Cue-approach training was found to be effective in influencing choice behavior at an immediate test and the preference shift was shown to persist over two months after the longest cue-approach training employed. In the studies described in this chapter, we spaced cue-approach training trials over two days to test the effects of this training schedule on the maintenance of the preference shift one week and one month after initial training.

One of the oldest and most reliable findings in research on human learning is the spacing effect. Ebbinghaus (1913) was the first to report, over 100 years ago, the benefits of spacing trial presentations in time during learning on

subsequent retrieval strength. Hundreds of studies have since established the spacing effect as a potent tool to improve memory retention (for review, see Carpenter et al., 2012; Cepeda et al., 2006). Information studied across multiple sessions spaced out in time is often better learned than information studied in the same amount of time in a single session. When Reynolds and Glaser (1964) taught participants biology terms over multiple consecutive repetitions (massed learning) or spaced review over time with other learning tasks in between (spaced learning), they found that spacing review over time produced significantly better retention of the material. Meta-analysis of the spacing effect in verbal learning tasks revealed that spaced (vs. massed) learning of items consistently leads to better long-term retention (Cepeda et al., 2006).

Researchers have also manipulated the lag or length of spacing between study presentations. The lag effect refers to improvements in memory performance for information that was repeated over longer lags compared to information repeated over shorter lags. Madigan (1969) gave participants lists of words, some of which were presented twice. The lag, or number of intervening words between the two presentations, varied. Recall for repeated words improved with longer lags. Here, for the sake of simplicity, we refer more generally to the spacing effect as the benefit of longer spacing on memory retention, where spaced training trials are distributed over longer time periods and massed trials are distributed over shorter time periods.

Recent work suggests that retrieval is a powerful encoding event and that it is more effective when retrieval is difficult (Benjamin and Tullis, 2010).

The longer the time lapse between study presentations, the harder it is to retrieve the memory of the last presentation. Given that delayed retrieval is more likely to be difficult than immediate retrieval, spacing study presentations should strengthen the memory trace for the learned behavior. Thus the spacing effect seems to be a general feature of learning and this has been demonstrated using several types of memory tasks. Lee and Genovese (1988) conducted a meta-analysis examining the effects of spacing practice on motor skills. They found that spaced practice enhances acquisition of motor skills compared to massed practice but more importantly it resulted in greater retention of motor skills compared to massed practice.

Spacing strategies have been successfully implemented to reduce the return of fear in treatment of anxiety disorders (Tsao and Kraske, 2000). Participants with public speaking anxiety who underwent a spaced schedule of exposure therapy experienced less return of fear at one-month follow-up than matched participants who followed a massed therapy schedule. Spacing treatment sessions holds great promise to help maintain behavioral change over the long term. To our knowledge, this strategy has not yet been applied to other behavioral change efforts outside the fear domain.

6.2 General Method

6.2.1 Overview

In the studies reported in this chapter, we spaced cue-approach training trial presentations over two consecutive days to test whether spacing improves

the maintenance of a shift in choice behavior. In the standard cue-approach task, participants are cued to press a button on the keyboard with a neutral tone that sounds a variable time averaging 750 ms after the food stimulus appears on the screen. In choices between two items that were equated for pre-experimental preferences, participants tend to choose items associated with the tone and button press (Schonberg et al., 2014a).

To facilitate discussion of methods and results across the three studies presented in this chapter, we define a Spaced item as an item that appeared on both days of cue-approach training (i.e. half their training phase presentations were on day 1 and the other appeared on day 2). We define Massed items as items that were trained on a single day, i.e. all the training phase presentations appeared on the same day. We define within-session lag as the average number of intervening items between presentations of a particular item on one day.

In the three studies reported here, we tested the effect of spacing cue-approach training trials over two consecutive days on the retention of the shift in choice behavior over one month. Additionally, we tested effects of the order in which Massed items appeared, true massing (i.e. zero within-session lag) and varying within-session lag for Spaced items in three studies.

6.2.2 Participants

75 healthy young participants completed three spacing of cue-approach training studies. Table 6.1 summarizes participant demographic characteristics for the three studies. No statistical tests were run a priori to determine sample

sizes, but the latter are similar to previous studies and were determined prior to data collection.

Study	N	Age (Mean ± SD)	Gender (F/M)	BMI (Mean ± SD)
6.1	25	20.7 ± 2.4	19/6	22.7 ± 4.4
6.2	25	20.6 ± 2.2	19/6	22.7 ± 3.1
6.3	25	22.2 ± 3.0	18/7	23.8 ± 4.4

Table 6.1: *Demographic details for spacing of cue-approach studies in chapter 6. SD (Standard Deviation). BMI (Body Mass Index).*

All participants had normal or corrected-to-normal vision, no history of psychiatric, neurologic or metabolic illness, no history of eating disorders, no food restrictions and were not taking any medication that would interfere with the experiment. Participants were informed that the goal of the experiment was to study food preferences and were asked to refrain from eating or drinking anything except water for four hours prior to each of their visits to the laboratory. The study was approved by the institutional review board (IRB) at the University of Texas at Austin and all participants gave informed consent.

6.2.3 Task

6.2.3.1 Auction

First, participants took part in an auction that was identical to that described in section 2.2.2.1 (Figure 6.2A). This auction allowed us to obtain a

measure of willingness-to-pay (WTP) for each of 60 appetitive junk food items per participant.

6.2.3.2 Item selection

Food items were rank ordered based on WTP from highest to lowest (Figure 6.1A). High-value items were placed in one of four training conditions in a 2 x 2 design (Go/NoGo x Spaced/Massed, Figure 6.1B) to allow for four different comparisons at probe: 1) Massed Go vs. NoGo, 2) Spaced Go vs. NoGo, 3) Spaced vs. Massed NoGo, 4) Spaced vs. Massed Go. Each pair type at probe was composed of nine unique pairs. This item selection procedure ensured that items that were paired during probe were equated for WTP such that participants should be indifferent to the choice between items in each pair given their stated pre-experimental preferences. In order to ensure that only 25% of all trials were Go trials, in accordance with standard cue-approach training, we included several low-value items (bottom half in Figure 6.1A) as Spaced and Massed NoGo items during training, but these items were never seen during probe. Item assignment to each of the four training conditions for items that appeared during probe was counterbalanced across participants.

6.2.3.3 Training

After completing the auction, participants started cue-approach training. They were asked to press a button on the keyboard as quickly as possible when they heard an infrequent tone (Figure 6.2B). The general cue-approach

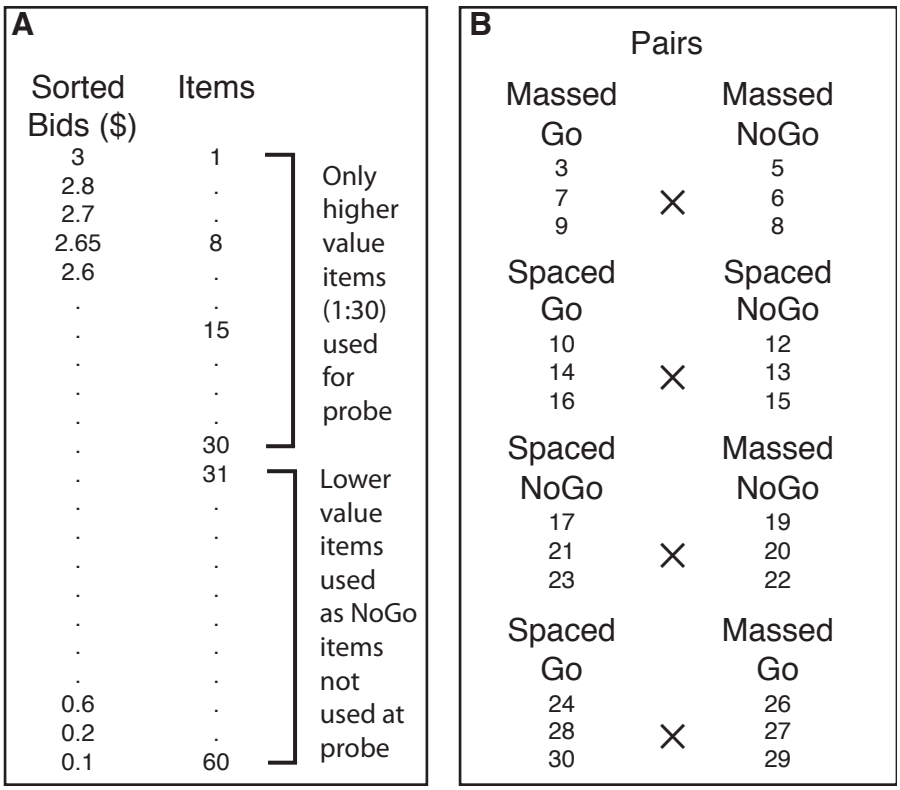

Figure 6.1: *Sorting and pair matching procedure used for studies 6.1, 6.2 and 6.3. Items are rank ordered based on bid obtained in the auction (Figure 2.1A). Only higher valued items (rank orders 3 to 30) are selected for use in the probe phase. Random selection of lower valued items (rank orders 31 to 60) are used as NoGo items during training but are not seen during probe. Items are assigned to one of four training conditions (Go/NoGo Spaced vs. Massed and Spaced/Massed Go vs. NoGo). Item condition assignments are counterbalanced across participants.*

training procedure is described in detail in section 5.2.2.4 and in Schonberg et al. (2014a). The tone appeared on average 750 ms after the food stimulus appeared on the screen and this Go signal delay (GSD) was adjusted using a staircase procedure to ensure that the participants would only achieve roughly 75% Go success, i.e. pressing the button after the tone sounds, but before the

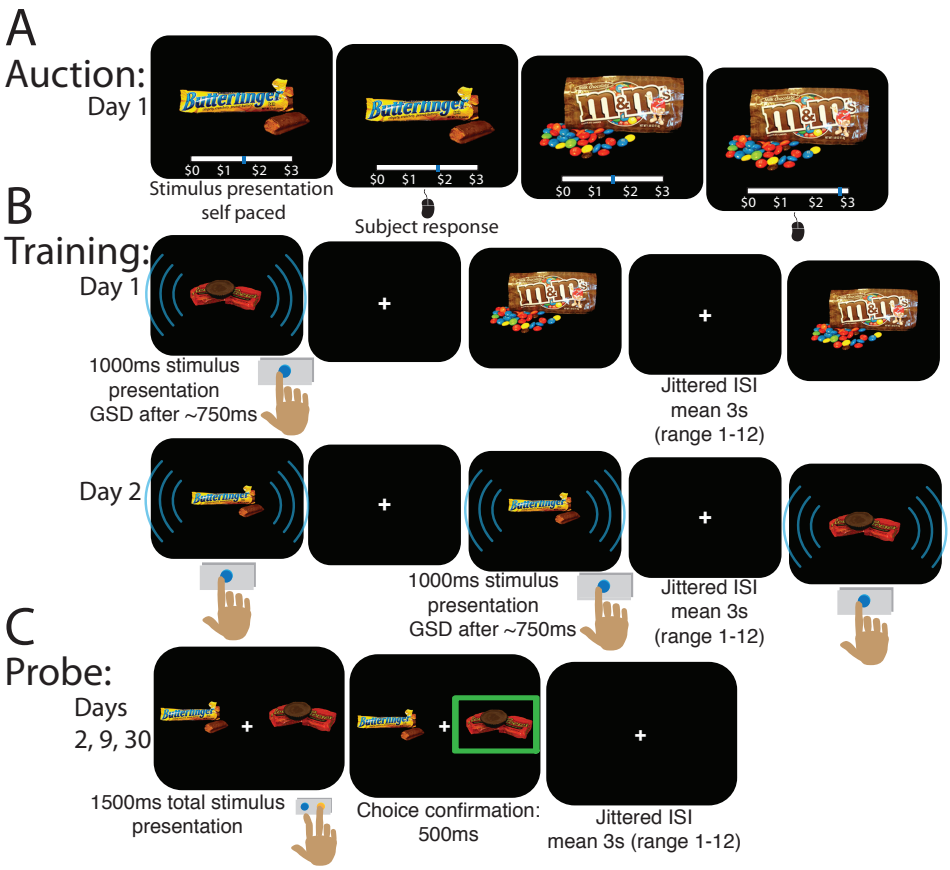

Figure 6.2: *Spacing of cue-approach training trials task procedure. A) Participants first take part in an auction. Food items are then rank ordered based on WTP and assigned to one of four conditions (Figure 6.1). B) Participants are then asked to observe the items and to press a button as quickly as possible only when they hear an infrequent tone (GO items). The tone sounds at a variable time after the food stimulus appears on the screen (GO signal delay [GSD]). GSDs are adjusted using a staircase procedure. Spaced items are seen on both day 1 and day 2 of training (e.g. Reese's peanut butter cups). Massed items are trained only on one of the days (e.g. M&Ms trained only on day 1 or Butterfinger trained only on day 2). C) Participants then choose between two items that are matched for WTP but differ on Go/NoGo or Spaced/Massed status for consumption in a probe phase. Participants then return for two follow-up probes one week and one month later.*

food stimulus disappears from the screen a fixed one second after the onset of a food stimulus. In all studies 12 out of a total of 48 items were consistently associated with a tone (Go items) during the training phase, which spanned two consecutive days. Items were either trained all on the same day (Massed items) or had half their training presentations on day 1 and the rest of the training presentation on day 2 (Spaced items). All items were presented a total of 12 times during training. The three studies in chapter 6 differ on the days on which Massed items are trained (Table 6.2). These studies were designed to test potential primacy and recency effects as well as lag effects on choice during probe following spaced cue-approach training.

Study	Day 1				Day 2			
	Spaced		Massed		Spaced		Massed	
	Items	Pres.	Items	Pres.	Items	Pres.	Items	Pres.
6.1	24	6	0	0	24	6	24	12
6.2	24	6	24	12	24	6	0	0
6.3	24	6	12	12	24	6	12	12

Table 6.2: *Number of items (Items) and number of presentations (Pres.) trained on for Spaced and Massed items on Day 1 and Day 2 of cue-approach training phase (Figure 6.2B) for all studies in chapter 6.*

6.2.3.4 Probe

After filling out a computer adapted version of BIS-11 (Patton et al., 1995), participants were presented with pairs of items that were matched for WTP and they were asked to choose one on each trial (Figure 6.2C). They

were told that a single trial at the end of the session would be selected and honored for real, meaning they would receive that item to eat. Four types of pairs were formed based on training (Figure 6.1). Each pair type was made up of nine unique pairs. Each unique pair was formed from three items, each paired with three other items with similar WTP but differed on one of the two factors: spacing or tone-pairing. (See Figure 6.1B.)

One week later, participants returned for a third visit. They performed another probe phase with the same setup but randomized trial order. They then took part in another auction. The second auction allowed us to look into any changes in WTP due to training. Finally, they provided simple demographic information and filled out the series of online questionnaires described in section 2.2.2.4.

Approximately one month after the first visit, participants were asked to return to the lab for a fourth visit. This visit was structured the same as the third visit, but they filled out a shorter set of questionnaires. Visits three and four allowed us to examine the effectiveness of spaced cue-approach training on the maintenance of choice preference for Go items and any induced choice preference for Spaced items.

6.2.4 Analysis

6.2.4.1 Probe

We hypothesized that distributing cue-approach training over two consecutive days would induce lasting preference change, in the form of greater

choice of Spaced Go items. To test our hypothesis, we performed repeated-measures logistic regression to compare the odds of choosing Spaced to Massed items as well as Go to NoGo items against equal odds. We ran the regression separately for each pair type (Spaced Go vs. Massed Go, Spaced NoGo vs. Massed NoGo, Spaced Go vs. Spaced NoGo and Massed Go vs. Massed NoGo) and for each probe (immediate, one week and one month follow-ups). To test for differences in reaction time (RT) during choices, we ran repeated-measures linear regression for each pair type and each probe separately.

6.2.4.2 Auction

To look at any change in the subjective value placed on individual items due to spaced cue-approach training, we used repeated-measures linear regression to test the two-way interaction between time (first, second [at one week follow-up] and third [at one month follow-up] auctions) and training conditions (Spaced/Massed Go or NoGo and Spaced or Massed Go/NoGo) on WTP within each pair type separately. This interaction tests whether the change in WTP over time is different for Spaced and Massed or Go and NoGo items. P values for the effects in the mixed models were calculated using the Kenward-Roger approximation for degrees of freedom (Kenward and Roger, 1997).

6.3 Study 6.1

We conducted this study to test whether spacing cue-approach trials over two days while expanding the within-session lag from day 1 to day 2 and presenting Massed items only on day 2 helped preserve the choice of Go over NoGo items one month after the end of training. We also tested whether this spacing and massing schedule induced a choice preference for Spaced over Massed items.

6.3.1 Method

During cue-approach training, participants in study 6.1 were trained on all Massed items on day 2 of training, i.e. all training presentations of all Massed items appeared only on day 2. Only half the training presentations of all Spaced items were presented during day 1. The second half of the training presentations of all Spaced items appeared on day 2. Within-session lag for Massed items was shorter ($\sim$ 36 items) than for Spaced items ($\sim$ 72 items). Within-session lag for Spaced items expanded from day 1 ($\sim$ 24 items) to day 2 ($\sim$ 72 items). Auction and probe procedures remained the same across studies.

6.3.2 Results and Discussion

Spaced Go items were chosen over Spaced NoGo items at an immediate probe following cue-approach training (second black bar from the left in Figure 6.3, see Table 6.3 for all statistics). Participants chose Spaced Go

items faster than they chose Spaced NoGo items at an immediate probe ($p = 0.03$). This preference for Spaced Go over Spaced NoGo items decreased but remained significant one month after the end of cue-approach training (second white bar from the left in Figure 6.3). At a one month follow-up probe, RT for choice of Spaced Go and for choice of Spaced NoGo did not differ ($p = 0.6$). Similarly, the preference for Massed Go over Massed NoGo items appeared to decrease over time, while choice of Massed Go was significant at the immediate probe but decreased to non-significant at the one month follow-up probe (left-most three bars in Figure 6.3). However, there was no interaction between pair type (Spaced/Massed Go vs. NoGo) and probe time (immediate/one month follow-up) on choices of Go items at probe. RT for choice of Massed Go was lower than for choices of Massed NoGo at both probes (p's < 0.03). Taken together, these results suggest that employing the spacing schedule in study 6.1 was of only very marginal benefit to help maintain choice of Go over NoGo items over the long term.

Participants did not choose Spaced Go over Massed Go items at an immediate probe (rightmost black bar in Figure 6.3). However, the choice of Spaced Go over Massed Go increased at the one month follow-up probe (rightmost white bar in Figure 6.3). There was no effect of spacing on choice of Spaced NoGo over Massed NoGo at the immediate probe. The lack of choice of Spaced NoGo over Massed NoGo was maintained at the one month follow-up (third set of bars from the left in Figure 6.3). There was only a marginal interaction between pair type (Spaced vs. Massed Go/NoGo) and probe time

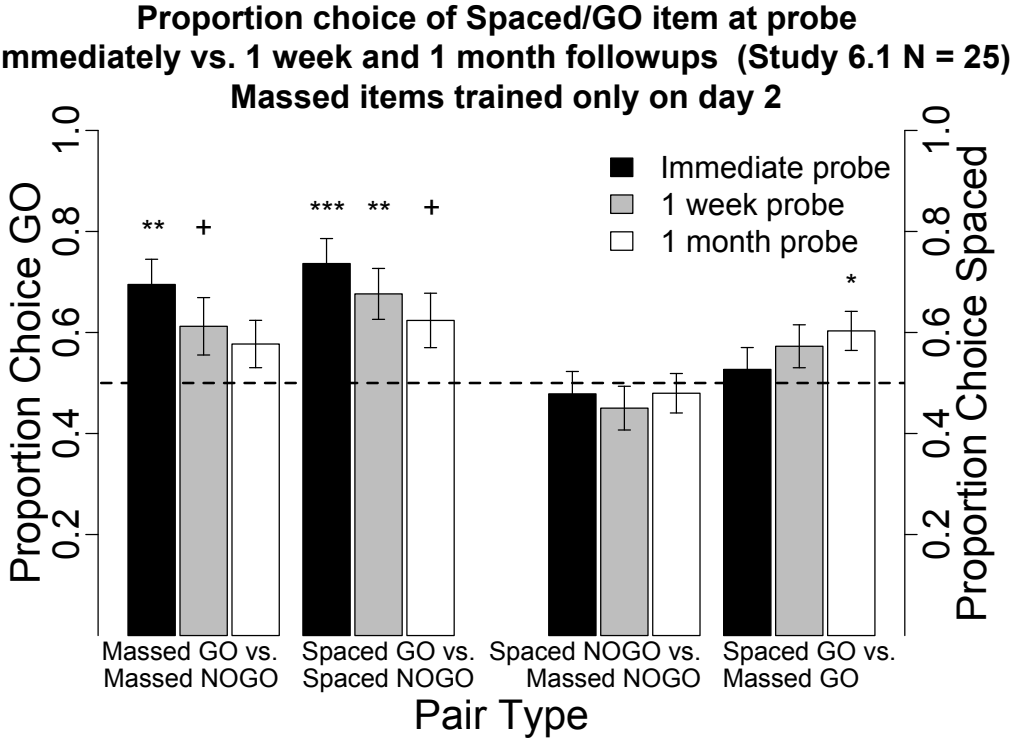

Figure 6.3: *Behavioral results at probe for spacing of cue-approach training study 6.1. Proportion choice of the the Go vs. NoGo item (six bars on the left) and proportion choice of Spaced vs. Massed item (six bars on the right) at probe immediately after training (black bars), one week (grey bars) and one month later (white bars). All error bars reflect one standard error of the mean (SEM).* $^{+}$ *:* $p < 0.05$*,* $*$ *:* $p < 0.01$*,* $**$ *:* $p < 0.001$*,* $***$ *:* $p < 0.0001$ *in two-tailed repeated measures logistic regression for odds of choosing Go to NoGo or Spaced to Massed against equal odds.*

(immediate/one month follow-up) on choices of Go items at probe ($p = 0.09$). There were no differences in RTs for choices of Spaced over Massed items (p's > 0.07 at either probe). These results suggest that spacing cue-approach trials over two days and expanding the within-session lag from day 1 to day 2 induces

a shift in preferences for Spaced over Massed items, but only if said items are associated with a Go tone during training.

Pair Type	Probe	Proportion	O.R	C.I	p-value	X p
Massed Go vs.	immediate	70%	3.23	[1.71 6.09]	0.0003	0.9
Massed NoGo	1 month	58%	1.45	[0.93 2.26]	0.1	
Spaced Go vs.	immediate	74%	5.04	[2.38 10.67]	< 0.0001	
Spaced NoGo	1 month	62%	2.27	[1.18 4.36]	0.01	
Spaced NoGo vs.	immediate	48%	0.90	[0.61 1.34]	0.6	0.09
Massed NoGo	1 month	48%	0.92	[0.66 1.27]	0.6	
Spaced Go vs.	immediate	53%	1.13	[0.78 1.65]	0.5	
Massed Go	1 month	60%	1.60	[1.14 2.24]	0.007	

Table 6.3: *Descriptive statistics for probe phase behavior in study 6.1. Proportion choice of Go over NoGo or choice of Spaced over Massed. Odds ratio (O.R) for choice of Spaced to Massed or Go to NoGo. Confidence interval (C.I) on odds ratio and p-value for odds of choosing Spaced/Go item against equal odds. Interaction p-value (X p) of pair type by probe time on odds of choosing Go to NoGo (top) or Spaced to Massed (bottom).*

There were no significant effects of spacing cue-approach training on the subjective value placed on food items. For all pair types of interest, item WTPs decreased equivalently over time (main effect of probe number [initial, one week and one month follow-ups] p's < 0.0001, but no main effect of or interaction with item type [all p's > 0.07] on WTP). The overall decrease in WTP over time is likely due to regression toward the mean, given that all items in this analysis were high value items based on the first auction. Regression to the mean in WTP measures over time has been previously reported (Schonberg et al., 2014a). These results provide evidence that spacing cue-approach training trials does not appear to influence the subjective value placed on food items.

6.4 Study 6.2

Because memory for Spaced items in study 6.1 could be stronger due to primacy effects, we conducted study 6.2 to test whether spacing cue-approach trials over two days while contracting the within-session lag from day 1 to day 2 and presenting Massed items only on day 1 (thus eliminating the primacy of Spaced item presentation) helped preserve the choice of Go over NoGo items one month after the end of training. We also tested whether this spacing and massing schedule induced a choice preference for Spaced over Massed items.

6.4.1 Method

Participants in study 6.2 were trained on all Massed items only on day 1 of training, i.e. all training presentations of all Massed items took place on day 1. Only half the training presentations of all Spaced items took place on day 1. The second half of the training presentations of all Spaced items were presented during day 2. Within-session lag for Massed items was shorter ($\sim$ 36 items) than for Spaced items ($\sim$ 72 items). Within-session lag for Spaced items contracted from day 1 ($\sim$ 72 items) to day 2 ($\sim$ 24 items).

6.4.2 Results and Discussion

Participants in study 6.2 chose Spaced Go over Spaced NoGo items at a probe that took place immediately following cue-approach training (second black bar from the left in Figure 6.4, see Table 6.4 for all statistics). Participants chose Spaced Go items faster than they chose Spaced NoGo items at

an immediate probe ($p = 0.0002$). This preference for Spaced Go over Spaced NoGo items decreased significantly one month after the end of cue-approach training (second white bar from the left in Figure 6.4). RT for choice of Spaced Go items was lower than for choice of Spaced NoGo items at the one month follow-up probe ($p = 0.03$). Similarly, the preference for Massed Go over Massed NoGo items appeared to decrease over time, whereas choice of Massed Go items was significant at an immediate probe but decreased significantly at the one month probe (leftmost three bars in Figure 6.4). However, there was no interaction between pair type (Spaced/Massed Go vs. NoGo) and probe time (immediate/one month follow-up) on choices of Go items at probe. RT for choice of Massed Go items did not differ from RT for choices of Massed NoGo items at both probes (p's > 0.2). These results again suggest that spacing cue-approach training trials over two days and massing items on a single day does not seem to benefit maintenance of Go over NoGo item choice over the long term.

There was no effect of spacing on choice of Spaced Go over Massed Go items at either the immediate or the one month follow-up probes (rightmost set of bars in Figure 6.4). Participants chose Spaced NoGo and Massed NoGo items equivalently at an immediate probe (third black bar from the left in Figure 6.4). However, at the one month follow-up probe, choice of Spaced NoGo over Massed NoGo items increased (third white bar from the left in Figure 6.4). There was a marginal interaction between pair type (Spaced vs. Massed Go/NoGo) and probe time (immediate/one month follow-up) on

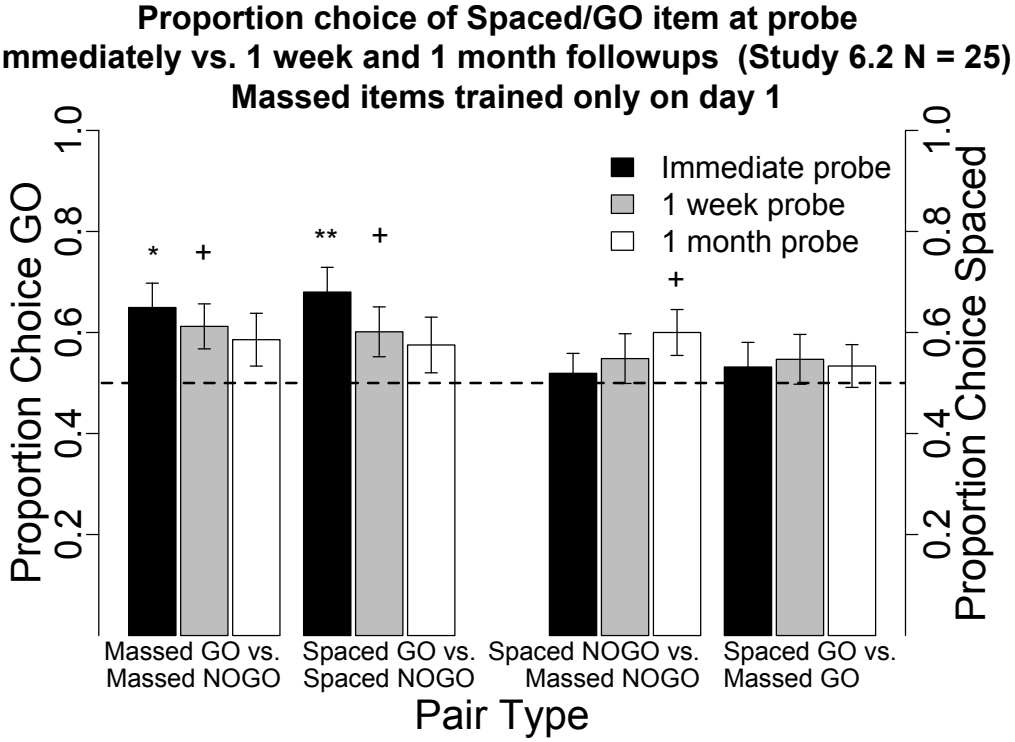

Figure 6.4: *Behavioral results at probe for spacing of cue-approach training study 6.2. Proportion choice of the Go vs. NoGo item (six bars on the left) and proportion choice of the Spaced vs. Massed item (six bars on the right) at probe immediately after training (black bars), one week (grey bars) and one month later (white bars). All error bars reflect one standard error of the mean (SEM).* $^{+}$ *:* $p < 0.05$*,* * *:* $p < 0.01$*,* ** *:* $p < 0.001$ *in two-tailed repeated measures logistic regression for odds of choosing Go to NoGo or Spaced to Massed against equal odds.*

choices of Go items at probe (p = 0.08). There were no differences in RTs for choices of Spaced and Massed items (p's > 0.1 at either probe). These results suggest that spacing cue-approach trials over two days and reducing the within-session lag from day 1 to day 2 induces a shift in preferences for Spaced over Massed items, but only if said items are not associated with a Go

tone during training.

Pair Type	Probe	Proportion	O.R	C.I	p-value	X p
Massed Go vs.	immediate	65%	2.23	[1.32 3.77]	0.003	
Massed NoGo	1 month	59%	1.68	[0.95 2.99]	0.08	0.3
Spaced Go vs.	immediate	68%	2.62	[1.53 4.49]	0.0005	
Spaced NoGo	1 month	58%	1.50	[0.81 2.78]	0.2	
Spaced NoGo vs.	immediate	52%	1.08	[0.78 1.51]	0.6	
Massed NoGo	1 month	60%	1.60	[1.06 2.41]	0.03	0.08
Spaced Go vs.	immediate	53%	1.17	[0.75 1.84]	0.5	
Massed Go	1 month	53%	1.18	[0.81 1.71]	0.4	

Table 6.4: *Descriptive statistics for probe phase behavior in study 6.2. Proportion choice of Go over NoGo or choice of Spaced over Massed. Odds ratio (O.R) for choice of Spaced to Massed or Go to NoGo. Confidence interval (C.I) on odds ratio and p-value for odds of choosing Spaced/Go item against equal odds. Interaction p-value (X p) of pair type by probe time on odds of choosing Go to NoGo (top) or Spaced to Massed (bottom).*

Spacing cue-approach training had no significant effect on the subjective value placed on food items. For all pair types of interest, item WTPs decreased equivalently over time (main effect of probe number [initial, one week and one month follow-ups] p's < 0.0001, but no main effect of or interaction with item type [all p's > 0.4] on WTP). These findings confirm that spacing cue-approach training trials does not seem to influence the subjective value placed on food items.

Study 6.2 was conducted in order to test whether recency of Spaced items had an effect on choices of Spaced vs. Massed items. In Study 6.1, choices of Spaced over Massed items could be interpreted as a primacy rather than a spacing effect given that Spaced items were seen earlier in the experiment on day 1 compared to Massed items, which were not seen until day 2

in Study 6.1. We find that choices of Spaced over Massed items increase as time elapses in both studies, although this increase in Spaced choice effect shifts from Go items in Study 6.1 (primacy of Spaced items) to NoGo items in Study 6.2 (recency of Spaced items). There appears to be a complex relationship between Go status and primacy vs. recency of Spaced items. More studies are needed to fully dissociate this relationship.

6.5 Study 6.3

In studies 6.1 and 6.2, items were not truly massed. True massing is defined as training repetitions with zero within-session lag, meaning training repetitions for a particular Massed item are consecutive, with no other item presentations in between. In studies 6.1 and 6.2, Massed items had half the within-session lag of Spaced items (which was higher than zero), but all training of Massed items occurred on only one of the two days. We conducted study 6.3 to test whether spacing cue-approach trials over two days while maintaining the same within-session lag from day 1 to day 2, truly massing items (training with zero within-session lag) and presenting Massed items on both day 1 and day 2 helped preserve the choice of Go over NoGo items one month after the end of training. We also tested whether this spacing and massing schedule induced a choice preference for Spaced over Massed items.

6.5.1 Method

Participants in study 6.3 had all 12 presentations of half the Massed items appear on day 1 of training and all 12 presentations of the second half of Massed items appear on day 2. Half of the presentations of all Spaced items were presented during day 1 and the second half of presentations of all Spaced items were presented during day 2. Massed items were truly massed with zero within-session lag (i.e. presentations of a particular Massed item were presented consecutively with no other intervening items). Within-session lag for a particular Spaced item averaged 48 items and remained the same from day 1 to day 2.

6.5.2 Results and Discussion

Participants in study 6.3 chose Spaced Go over Spaced NoGo items consistently over time (second set of bars from the left in Figure 6.5, see Table 6.5 for all statistics). Participants chose Spaced Go items faster than they chose Spaced NoGo items at both probes (p's < 0.007). However, participants consistently had no preference for Massed Go over Massed NoGo items over time (leftmost three bars in Figure 6.5). There was a main effect of pair type (Massed/Spaced Go vs. NoGo, $p = 0.03$), but no main effect of probe time (immediate/one month follow-up) or interaction between the two on choices of Go over NoGo items. RT for choice of Massed Go and RT for choices of Massed NoGo did not differ at either probe (p's > 0.07). These results suggest that spacing cue-approach trials over two days and maintaining the same within-

session lag across days offer significant benefit to the maintenance of Spaced Go over Spaced NoGo choice over time. However, truly massing cue-approach training trials and presenting Massed items consecutively with no intervening items eliminates the Go choice effect altogether. As we will discuss below, this could be due to an increase in preference for Massed NoGo items that counteracts the regularly induced preference for Go items.

Pair Type	**Probe**	**Proportion**	**O.R**	**C.I**	**p-value**	**X p**
Massed Go vs.	immediate	52%	1.14	[0.64 2.04]	0.7	0.4
Massed NoGo	1 month	47%	0.85	[0.46 1.57]	0.6	
Spaced Go vs.	immediate	70%	2.77	[1.76 4.38]	< 0.0001	
Spaced NoGo	1 month	69%	2.64	[1.66 4.19]	< 0.0001	
Spaced NoGo vs.	immediate	29%	0.32	[0.19 0.53]	< 0.0001	0.7
Massed NoGo	1 month	32%	0.38	[0.23 0.62]	0.0001	
Spaced Go vs.	immediate	54%	1.20	[0.72 1.99]	0.5	
Massed Go	1 month	55%	1.24	[0.67 2.3]	0.5	

Table 6.5: *Descriptive statistics for probe phase behavior in study 6.3. Proportion choice of Go over NoGo or choice of Spaced over Massed. Odds ratio (O.R) for choice of Spaced to Massed or Go to NoGo. Confidence interval (C.I) on odds ratio and p-value for odds of choosing Spaced/Go item against equal odds. Interaction p-value (X p) of pair type by probe time on odds of choosing Go to NoGo (top) or Spaced to Massed (bottom).*

There was no effect of spacing on choice of Spaced Go over Massed Go items at either probe (rightmost set of bars in Figure 6.5). RT for choice of Spaced Go was lower than for choice of Massed Go items at the immediate ($p = 0.007$), but not at the one month follow-up probe ($p = 0.9$). However, participants consistently chose Massed NoGo over Spaced NoGo items at all probes (third set of bars from the left in Figure 6.5). RT for choice of Massed

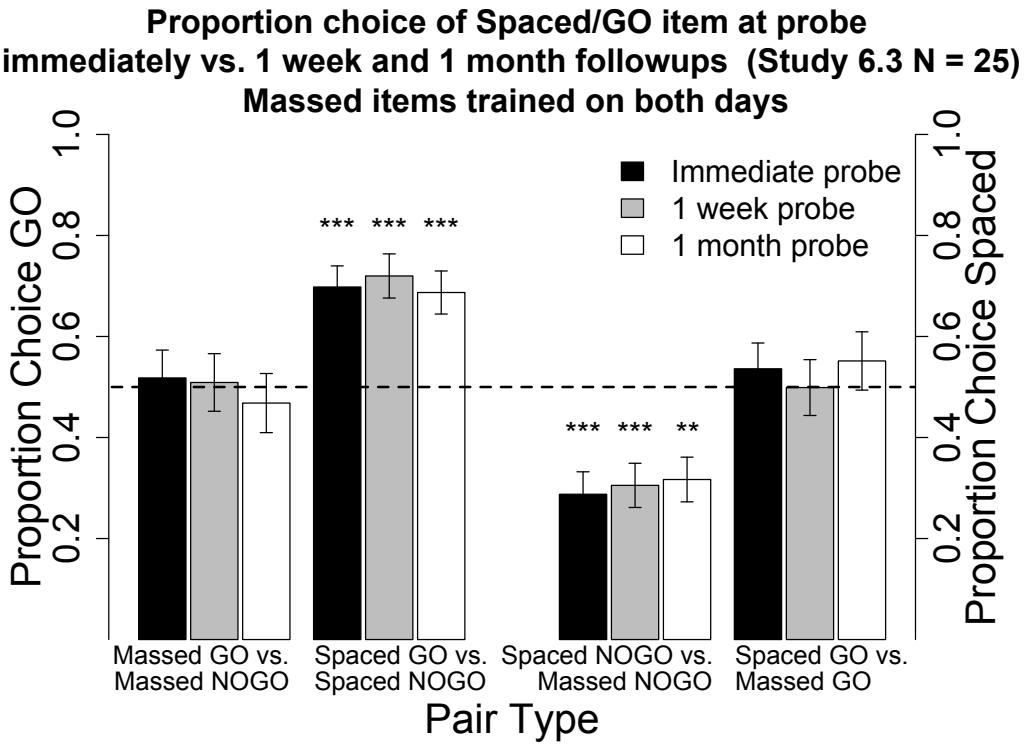

Figure 6.5: *Behavioral results at probe for spacing of cue-approach training study 6.3. Proportion choice of the Go vs. NoGo item (six bars on the left) and proportion choice of the Spaced vs. Massed item (six bars on the right) at probe immediately after training (black bars), one week (grey bars) and one month later (white bars). All error bars reflect one standard error of the mean (SEM). ** : $p < 0.001$, *** : $p < 0.0001$ in two-tailed repeated measures logistic regression for odds of choosing Go to NoGo or Spaced to Massed against equal odds.*

NoGo was lower than for choice of Spaced NoGo at the immediate ($p = 0.0004$), but not at the one month follow-up probe ($p = 0.9$). These results suggest that truly massing items induces a strong and lasting preference for Massed over Spaced items, but only if said items were not associated with a Go cue during cue-approach training.

There were no significant effects of spacing cue-approach training on the subjective value placed on food items. For all pair types of interest, item WTPs decreased equivalently over time (main effect of probe number [initial, ome week and one month follow-ups] p's < 0.0001, but no main effect of or interaction with item type [all p's > 0.1] on WTP). These results replicate findings from studies 6.1 and 6.2, which confirms that spacing cue-approach training trials has no effect on the subjective value placed on food items.

6.6 General Discussion

Previous work has established cue-approach training as a reliable method to influence choice by targeting automatic processes rather than relying on effortful control of behavior (Schonberg et al., 2014a). The shift in preference for appetitive junk food items was maintained over two months following the longest training tested. In the current studies, we sought to improve the long term maintenance of a change in choice behavior by spacing training trials over two consecutive days.

Spacing cue-approach training trials overall had a more consistent effect on the maintenance of Go item choice preference over one month than massing training trials. More consistent spacing of item-auditory cue-motor response pairing repetitions (i.e. equal within-session lag) across two consecutive days of training seems to have the most benefit for maintenance of Go item preference. The proportion choice of Spaced Go over Spaced NoGo items is highest at the one month follow-up probe in study 6.3, where the two training sessions on

each of the two days are equal (i.e. equal within-session lag) and a Spaced item appeared on average every 48 trials on either day. In Studies 6.1 and 6.2, the lag between pairings for Spaced items is asymmetric between the two days, with one day having a longer training session than the other. In the first two studies, Spaced items appeared on average every 24 trials on one day and every 72 trials on the other day.

Massing cue-approach training trials on a single day weakens the maintenance of the Go choice effect, with no significant choice of Massed Go over Massed NoGo at the one month follow-up, across studies. Truly massing training trials so that trials are presented consecutively, with no intervening other items (i.e. zero within-session lag), eliminates the Go choice effect (leftmost bars in Frigure 6.5). Additionally, truly massing trial presentations produces a lasting preference for Massed NoGo items, with consistent choice of Massed NoGo over Spaced NoGo at all three probes (third set of bars from the left in Frigure 6.5). This preference for zero within-session lag Massed NoGo items in study 6.3 may be interfering with the regularly observed preference for Go over NoGo items and may explain the lack of choice of Massed Go over Massed NoGo at all probes in study 6.3.

The order in which Massed items, or the expanding or contracting within-session lag for Spaced items, seems to have an effect on choice of Spaced over Massed items that interacts with their Go/NoGo status. Expanding the within-session lag from day 1 to day 2 as in study 6.1 (average lag for Spaced items on day 1 being 24 and 72 on day 2) increases the choice of Spaced Go

over Massed Go, but does not benefit the choice of Spaced NoGo over Massed NoGo items over time (6 rightmost bars in Frigure 6.3). On the other hand, contracting the within-session lag for Spaced items from day 1 to day 2 as in study 6.2 (average lag for Spaced items on day 1 being 72 and 24 on day 2) boosts the choice of Spaced NoGo over Massed NoGo, but does not increase the choice of Spaced Go over Massed Go items over time (6 rightmost bars in Frigure 6.4). As described previously, truly massing training trials with no lag for Massed items and maintaining the same within-session lag for Spaced items on both training days as in study 6.3 (with an average lag of 48 on both day 1 and day 2) benefits choice of Massed NoGo over Spaced NoGo items in a lasting manner. This massing schedule, however, does not appear to affect the choice of Spaced Go over Massed Go items (6 rightmost bars in Frigure 6.5).

Although spacing cue-approach training trials can influence choice, it does not seem to have an effect on the subjective value placed on food items. We have previously suggested that attentional and memory mechanisms are at play during cue-approach training (Schonberg et al., 2014a), although the contribution of each to choice and valuation remain unknown. Further work is needed to fully understand the role of memory during this task and its influence on choice behavior and valuation. Better characterization of the role of memory in this task may help optimize the spacing schedule during cue-approach training to yield the longest duration of behavioral change.

Previous research has determined that a lag of one day between study sessions was optimal for retention intervals of about a week to one month for

verbal learning tasks (Cepeda et al., 2006). For practical reasons, we chose to bring participants back for the final probe four weeks after the end of cue-approach training, thus opting for a between-session lag of one day in the current studies. This conforms to conventional wisdom in the field, i.e. that optimal between-study episode lag is around 10-20% of the retention interval (Carpenter et al., 2012). Further studies that vary lag for Spaced items will be needed to define the boundaries of the spacing effect in the cue-approach task.

Most studies to date on the spacing effect employ motor skill or verbal learning tasks and to our knowledge none have explored the spacing effect using a non-reinforced associative task such as the cue-approach task employed here. Pashler et al. (2007) have reported a lack of spacing effect using perceptual categorization tasks. Although more research is needed on the topic, it seems not all forms of learning benefit from spacing. Given the associative nature of the task employed here, we believe that spacing principles are likely to be applicable to the cue-approach task. More studies employing spacing in other forms of non-reinforced learning tasks are needed to fully understand the task characteristics that make spacing effective in improving long term performance in these types of tasks.

In conclusion, we propose that spacing cue-approach training trials may help maintain the change in preference for appetitive food over the long term. Although not widely adopted by clinicians, spacing strategies have proven useful in the treatment of anxiety disorders (Tsao and Kraske, 2000). Sev-

eral researchers have for some time advocated the implementation of spacing strategies in instruction, given its clear advantage for long-term memory retention and its applicability to academic goals (Dempster, 1988; Carpenter et al., 2012). Here we show that similar strategies may potentially be useful for attaining more common behavioral change goals such as maintaining healthy weight.

Chapter 7

General Discussion

The ability to change one's behavior is adaptive, as behavioral change allows one to adjust to dynamic environments. Fundamental features of learning, however, work against effortless and flexible behavioral change. This dissertation lays out a framework for the study of behavioral change within the confines of learning theory. Given that older behaviors tend to be stronger, more flexible and generalizable than newer-learned behaviors (Bouton, 2004), a two-pronged approach was adopted to attain behavior change. On the one hand we aimed to weaken old behavior, and on the other, we attempted to strengthen newer behavior. Additionally, given the limited long-term viability of methods that rely on active reinforcement to change behavior, we have focused our efforts on targeting automatic processes to achieve behavior change without relying on self-control, which is known to be fragile. In the preceding chapters, I described several novel task designs that have been met with variable success in achieving the common goal of shifting choice behavior. In several studies, we have also explored the neural mechanisms underlying successful behavior change using fMRI. We found that driving attention toward particular items at behaviorally relevant points in time during cue-approach training modulates the subjective value of individual food items. The cue-

approach task proves to be a robust method to influence choice behavior and holds great promise for the development of novel real-world behavioral change paradigms. Furthermore, we found that distributing cue-approach training trials over time helps the maintenance of the shift in choice behavior over the long term. We also attempted to update memories for choice within the reconsolidation window and to train inhibition in order to induce a change in behavior, but these efforts were met with limited success. More research is needed to define the task parameters necessary to induce a change in behavior by interfering with memory traces for certain actions within the reconsolidation window or training inhibition. In the following sections, I summarize our results and discuss their impact and potential for future research.

7.1 Mechanisms of reinforced training

In chapter 2 and Schonberg et al. (2014b), we described a novel extensive training paradigm where participants were rewarded for choosing a junk food that held a lower subjective value than the alternative. At a later choice phase, during which participants chose between fixed pairs for actual consumption, we found that less preferred items were chosen more often in trained pairs than in untrained pairs. This shift in choice behavior was associated with a decrease in reliance over the training period on a frontoparietal network of brain regions previously implicated in self-control. Additional imaging analyses provide evidence for the formation of stimulus-response associations over the training period. These findings point to a shift from reliance on goal-

directed to more habitual responding as overtraining progressed. These findings provide potential mechanistic explanations for the success of interventions that use financial incentives for dietary behavior change (Purnell et al., 2014, for review) and extend findings in the neuroeconomics literature as we show higher activation in brain regions similar to those we report for dieters with greater self-control (Hare et al., 2009).

For the study described in chapter 2, we developed a general framework within which to study behavioral change with a general task structure that allowed us to first obtain pre-experimental preferences on a participant by participant basis which then allowed us to strategically place stimuli in training conditions aimed at shifting preferences that are tested in a probe phase. This general framework was adopted in many of the subsequent studies discussed in this dissertation. The research described in chapter 2 is significant in that it is the first, to our knowledge, to employ this kind of contingency management paradigm to influence food choices, showing promise for the development of new interventions to influence real-world food choices. However, given the limited success of contingency management in stemming drug abuse over the long term (Higgins et al., 1995), the failure of effortful self-control, especially under stress or distraction (Baumeister et al., 1998) and the quasi inevitability of the recency-primacy shift or spontaneous recovery (Bjork, 2001; Bouton, 1993), maintenance of the shift in food choice behavior described in this study over the long term is questionable. Thus, we focused our latter efforts on targeting automatic processes to achieve lasting behavioral change.

7.2 Targeting automatic processes to weaken old behavior

Two main avenues to change behavior by weakening old responses through targeting automatic processes were attempted. One aimed to directly perturb memory traces for particular responses and the other was directed to train bottom-up inhibition. Our efforts on this front were not successful and our goals were not achieved, but adjustments to the implementation of these ideas could prove useful in future research. After summarizing our efforts to weaken older behavior in the following paragraphs, I will highlight possible paths for future research.

Memories are known not to be set in stone. Recall renders memories malleable and susceptible to updating (Nader et al., 2000). This mechanism, called reconsolidation, is adaptive, since organisms need flexibility to integrate new information from the environment to update their map of a changing world. Memory reconsolidation is a transient state and memories are fragile for only a number of hours after recall before they restabilize (see Besnard et al., 2012; Alberini and Ledoux, 2013; Reichelt and Lee, 2013, for review). In chapter 3, we sought to take advantage of this fundamental feature of memory to target choice behavior memory traces for updating during the reconsolidation window. We designed an ABA renewal paradigm, where participants learn to press one of two buttons to receive points 80% of the time for a number of neutral stimuli in context A. 24 hours later, participants underwent reversal learning in a second context B either ten minutes after a reminder

of the stimuli (within the reconsolidation window, 10min group) or six hours after a reminder (outside the reconsolidation window, 6hr group). We hypothesized that reversal learning within the reconsolidation window would disrupt renewal when participants chose between two button presses to the same stimuli under extinction conditions in a test when returned to context A on a third day. Although we observed significant renewal in the 6hr group, renewal was not significantly attenuated in the 10min group. To our knowledge, memory updating has not been demonstrated in the context of an appetitive choice paradigm. Previous research has shown that differences in task parameters that govern the reconsolidation process explain discrepancies in the literature related to memory updating (Piñeyro et al., 2014). Targeting memory reconsolidation has been adopted for the treatment of anxiety disorders such as PTSD (Debiec and Ledoux, 2006; Brunet et al., 2008) as well as in the appetitive domain in the treatment of drug abuse (Xue et al., 2012) and it shows great promise for broader adoption for more common behavior change goals. Although we were not successful in inducing a change in our studies, the research presented in chapter 3 may be used as a starting point to iterate on in future research in order to define the task parameters necessary to update a memory for choice behavior. For example, length (Piñeyro et al., 2014), responses required (Lee and Everitt, 2008b) and spatial context (Hupbach et al., 2008) during the reminder can be modified and may be key to successful memory updating in this task.

While memory reconsolidation has potential for achieving a shift in

choice behavior, we took a broad approach and studied multiple strategies to achieve our goal. Inhibition is a crucial feature of cognition and can be a bottom-up process (Verbruggen and Logan, 2008). We attempted to induce an automatic inhibitory signal to particular items by associating a stop-signal with them. In three studies presented in chapter 4, two of which were previously described in Schonberg et al. (2014a), we adapted the general framework we had previously developed in Schonberg et al. (2014b) and chapter 2 to include a stop-signal task for the training phase. Participants pressed a button every time an appetitive junk food item appeared on the screen. On 25% of trials, a stop-signal appeared after a variable delay following particular item onsets. Consistently associating a stop signal with particular stimuli has previously been shown to elicit an automatic inhibitory signal when the stimulus appears in absence of the stop-signal (Verbruggen and Logan, 2008; Lenartowicz et al., 2011). We hypothesized that training inhibition in this way would lead participants to avoid choosing items that had been associated with a stop-signal during the training phase in favor of items that were not associated with a stop-signal but of equal pre-experimental value. Although other groups were successful in influencing choices by associating stop-signals with particular items (Veling et al., 2013a; Wessel et al., in press), our efforts were not. More research is needed to better understand the stop-signal task parameters that govern choice effects following training of inhibition. The number of stimuli used and the timing of the stop-signal in particular might be key factors for successfully inducing avoidance behavior to particular items after

associating them with a stop-signal.

Although we were not successful in inducing a change in behavior by targeting memory updating and bottom-up inhibition, this line of research has high potential for the development of novel interventions for the treatment of impulsivity and anxiety disorders, but may also be useful in developing behavioral change paradigms to achieve more common goals such as losing weight.

7.3 Targeting automatic processes to strengthen new behavior

In addition to attempting to weaken old behaviors, we sought to strengthen new behavior and developed the cue-approach task, which is the functional mirror of the stop-signal task (Logan et al., 1984). The cue-approach task and initial findings are described in detail in Schonberg et al. (2014a). We used the same general framework we previously developed to study overtraining effects on choice behavior (chapter 2, Schonberg et al., 2014b). In the cue-approach task, participants passively view images of food items, except when they hear a tone. When they hear a tone, they are instructed to press a button on the keyboard as quickly as possible. The cue-approach task has been established as a robust method to influence choice. Participants consistently choose the item that had previously been associated with a tone over an item that had not but that is of equal pre-experimental preference. In chapter 5, we sought to apply advanced imaging analysis methods to better understand neural changes

during the training phase that predict choice effects at a later probe. We developed a cognitive localizer task that engages three cognitive processes thought to be engaged during cue-approach training. We hypothesized that changes in the engagement of these cognitive processes during cue-approach training would predict a shift in preferences at the probe phase. This research is significant in that it partially replicated previous imaging findings and established limits to the utility of training a classifier on fMRI data from one task (in our case the cognitive localizer task) and applying it to a vastly different task (in our case the cue-approach training task) in order to obtain the level of engagement of particular cognitive processes measured as estimates of classifier evidence. More research is needed to better understand the neural changes during cue-approach training that support a shift in choice behavior. However, behavioral variants of the cue-approach task not discussed in this dissertation have established that both a cue and a motor response are necessary, that the cue to press a button must be delayed and that the choice effect at probe is not specific to the trained motor effector. Taken together, these findings single out sustained attention during behaviorally relevant points in time as a modulator of subjective value. Previous research had already established a link between visual attention and choice preference (Krajbich and Rangel, 2011) and manipulation of visual attention has been shown to influence preferences (Shimojo et al., 2003; Armel et al., 2008). Additionally, focusing attention at behaviorally relevant points in time improves memory for task irrelevant information (Lin et al., 2010; Swallow and Jiang, 2010). The cue-approach task

takes advantage of selectively focusing attention at particular times to influence choice preference and presents a viable paradigm to potentially develop real-world interventions in support of health improvement goals.

At the outset of the project on which this dissertation is based, our goal has always been to examine ways to achieve long-term maintenance of a change in behavior. Although targeting automatic processes rather than relying on effortful control was more likely to achieve this goal (Marteau et al., 2012), we set out to explicitly explore strategies that further ensure the viability of a shift in behavior over the long term. We took inspiration from the declarative memory literature and spaced cue-approach trial presentations over two days and systematically probed choices between items that varied on either cue status or spacing immediately, one week and one month after the end of training. Previous research has established that spacing study sessions improves memory for studied information over the long term (Cepeda et al., 2006; Carpenter et al., 2012, for review). We have shown in chapter 6 that we can improve the maintenance of the basic cue-approach effect over one month by spacing cue-approach training trials over two days of training. The order in which items appear over the two days also appears to influence choice, but spacing has clear advantages in helping maintain a shift in choice behavior under several spacing configurations. Maintaining healthier behavior over a duration that spans months and years is essential to achieve most public health goals such as maintaining a healthy weight. Our findings suggest that any interventions that are developed that target automatic processes to strengthen

new behaviors may also benefit from spacing sessions over time, which will boost the persistence of new behavior over the long term.

7.4 Conclusions

The work presented in this dissertation provides a framework for studying mechanisms of behavioral change. Given the automaticity of mostly habitual everyday behavior, targeting automatic processes seems the best way to achieve lasting behavioral change. Memory updating and training inhibition are appealing prospects, but our findings suggest that more research is needed to refine the task characteristics that govern these strategies to induce positive behavior change. The cue-approach training task presents the most immediate promise for achieving this goal and may inspire the development of new interventions to influence real-world behavior. The exact neural mechanism by which cue-approach training modulates the subjective value of individual goods remains poorly understood and is an active area of research. However, results point to the importance of driving attention at behaviorally relevant points in time to perturb underlying subjective value for particular stimuli. This line of research can also help us better understand how value is constructed in the brain and provide new insights to the fundamentals of value-based decision making.

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